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Addressing the challenge of hip fracture fixation and prevention in old age

Preclinical and clinical studies assessing the osteoporotic femoral head

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Cover picture courtesy of the AO Foundation

To Steven Boonen

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3S

The audience
YOU

The reader

Patiënten

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List of abbreviations

3D	three dimensional
AB	aktiebolog (Swedish; private limited liability company)
AG	Aktiengesellschaft (German; private limited liability company)
ANOVA	analysis of variance
AO	Arbeitsgemeinschaft für Osteosynthesefragen
ARI	AO research institute
ASA	American society of anaesthesiologists
ASTM	American society for testing and materials
BMD	bone mineral density
CCD	caput collum diaphyseal angle
CI	confidence interval
CINAHL	cumulative index to nursing and allied health literature
cm	centimeter
CMBD	center for metabolic bone diseases
CT	computed tomography
DEXA	dual energy X-ray absorptiometry
DHS	dynamic hip screw
e.g.	exempli gratia
et al.	et alii
F	force
FWO	fonds wetenschappelijk onderzoek
FUTime	follow-up time
Ga	gauge
GEMU	geriatric assessment and management unit
GmbH	Gesellschaft mit beschränkter Haftung
H	height
HA	hydroxyapatite
Hz	hertz
i.e.	id est
Inc.	incorporated
IU	international unit
kN	kilo newton

K-wire	Kirschner-wire
L	length
MCU	multi-camera control unit
MeSH	medical subject heading
ml	milliliter
mm	millimeter
MTS	mechanical testing system
MTS corp	mechanical testing systems corporation
N	newton
NRS	non-randomized study
OR	odds ratio
pcf	pounds per cubic foot
PFN	proximal femoral nail
PFNA	proximal femoral nail antirotation
PMMA	polymethylmethacrylate
pQCT	peripheral quantitative computed tomography
RCT	randomized controlled trial
SD	standard deviation
W	width
TM	trade mark

General introduction

1. Definition and diagnosis of osteoporosis

Following the internationally agreed definition, osteoporosis is "a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue".[1] These structural changes in cortical and trabecular bone are clearly visible on the micro-CT (Computed Tomography) images of a normal (figure 1a) and an osteoporotic femoral head (figure 1b) (Images courtesy by Andrea Tami, AO (Arbeitsgemeinschaft für Osteosynthesefragen) Research Institute, Davos, Switzerland). These transverse slides through the femoral head show the larger trabeculae with thinner walls as well as the presence of more empty spaces in the osteoporotic specimen.

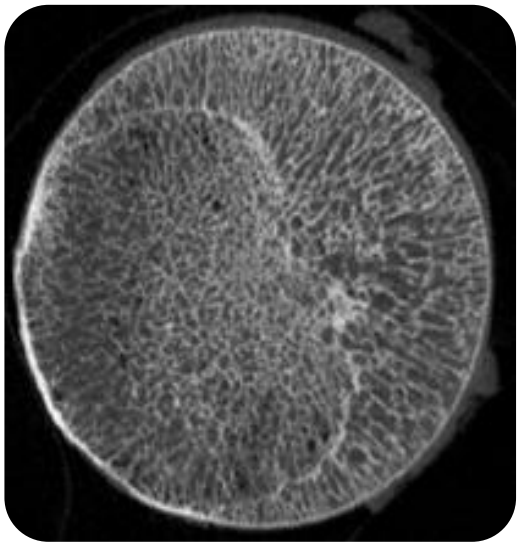

Figure 1a

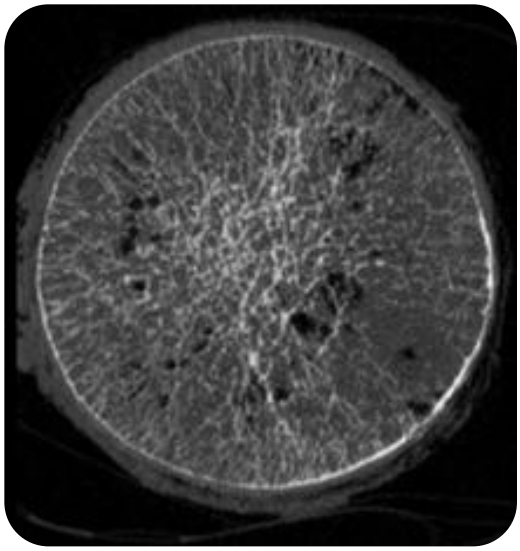

Figure 1b

When determining the corresponding bone mineral density by pQCT (peripheral Quantitative Computed Tomography), a measurement of volumetric bone mineral density is performed, resulting in a lower total, trabecular and cortical density for the osteoporotic specimen. In a clinical setting, bone quality measurement is performed by DEXA (Dual Energy X-Ray Absorptiometry)-scan. The alterations in osteoporotic bone morphology and subsequently bone density[1], lead to a higher risk for osteoporotic or fragility fractures. Of all fragility fractures, hip fractures constitute the most dramatic complication and are a major public health concern. Figure 2 displays the X-Ray image of a subtrochanteric fracture in a 95 years old lady. Take notice of

the low visibility of the bone with the same density as the calcifications in the femoral arteries.

Figure 2

2. Consequences of osteoporotic hip fractures for the individual patient

From a clinical perspective, the main consequences of fragility hip fractures are the associated morbidity, loss of quality of life, and mortality.[2,3] Up to 20-25% of fragility-related hip fracture patients die within the year following their fracture. Of those who do survive, up to 40% will not be able to return to their pre-fracture level of activities of daily living with institutionalisation for about 20% of patients because of the fracture and its functional consequences.[4] Moreover, recent studies show that the excess mortality after hip fractures persists over time, for both women and men.[5,6] Furthermore, it has been shown that there is an increased risk of sustaining a secondary osteoporotic fracture after a first vertebral, hip or shoulder fracture with the highest risk of secondary fractures occurring immediately after the first fracture.[7] The absolute and relative fracture risk following an initial fragility fracture is the highest in case of a preceding hip fracture.[8] For women, there is an absolute risk for a secondary fracture following a hip fracture of 89 (66-119) per 1000 person-years and a relative risk of 2.79 (2.06 – 3.77).[8] This finding might be explained by the loss of BMD (Bone Mineral Density) that occurs shortly after having sustained a hip fracture.

This loss of BMD might continue in the year following the fracture.[9] It was also shown that the only predictor of decrease in BMD after sustaining a fragility fracture is BMD at baseline.[10] Interestingly, more than 80% of hip fracture patients have previously undiagnosed secondary causes of bone loss of which vitamin D insufficiency, chronic kidney disease and calcium malabsorption are the most common.[11]

Besides the increased morbidity associated with secondary fractures, subsequent fractures also have a highly significant influence on mortality.[12] In a prospective cohort study on long term mortality following osteoporotic fractures, subsequent fracture was associated with an increased mortality hazard ratio of 1.91 (95% CI, 1.54 – 2.37) in women and 2.99 (95% CI, 2.11 – 4.24) in men. The fracture was only in 10.5% mentioned in death certificates as being directly related to the death of the patient. The major causes of death were cardiac (27%) and respiratory (26%) failure.[13] Finally, secondary hip fractures often are complex fractures and are more difficult to treat from a surgical point of view.

The impact of secondary fractures on the individual patient is high. Therefore fragility hip fracture treatment should not only focus on the treatment of the actual fracture, but also on the treatment of the underlying osteoporosis to reduce the refracture risk.[8]

3. Economic consequences of fragility hip fractures

During the last decades, a tremendous increase in the number of osteoporosis related hip fractures has been noticed due to the active aging of our population. This evolution will continue exponentially: in 2025, there will be an estimated three million annual incident hip fractures in the United States, creating direct medical costs of $ 25 billion.[14] These American numbers correspond to similar numbers of fragility hip fractures and related costs in Europe: in 2010 there was an incidence of 3.5 million osteoporotic fractures generating an economic burden of € 37 billion; these costs will increase by 25% in 2025.[15] It was calculated in a prospective cohort study with matched pair analysis that the costs of treating a hip fracture patient in Belgium are three times higher than those of caring for a patient without a fracture.[16]

4. The role of co-managed care and clinical pathways in fragility hip fracture treatment

During the last years, a lot of studies have been published supporting the role of co-managed care for fragility hip fracture patients.[12] It has become clear that an orthogeriatric collaboration, passing beyond just good fracture care, will lead to a better outcome especially for the very old patients suffering from multiple comorbidities.[17] Different models of co-managed care have been described, all based on a collaboration of surgeons and geriatricians, both more consultative as well as integrated care approaches.[18]

Furthermore it is clear that care pathways (also known as clinical pathways or critical pathways) play a beneficial role in general health care management and more specifically in the organization of the care for osteoporotic hip fracture patients.[19,20] As most of the orthogeriatric care models are based on multidisciplinary team work, aim at the integration of a package of evidence based key interventions and include an active follow-up, they correspond to the definition of care pathways.[21]

However, co-managed care and clinical pathways for fragility hip fracture patients as well, only focus on short term effects like length of stay and in-hospital or 30-days mortality.[12,22] Little information is available about long term mortality (at least 1 year postoperatively) and about fracture recurrence rates in the years following the first fracture.

5. Secondary fracture prevention

Despite existing guidelines and effective therapies, there is a lack of awareness of the incidence and potentially adverse outcomes of senile osteoporosis. The above-described unfavourable prognosis of osteoporotic hip fractures emphasizes the need for secondary fracture prevention. Both pharmacological as non-pharmacological interventions (e.g. falls prevention) can reduce the risk of recurrent fractures.[23]

With advancing age, calcium intake diminishes as well as the absorptive capacities of the body.[24] Due to insufficient sunlight exposure and decreased capacity of the skin to produce active vitamin D, vitamin D deficiency becomes more prevalent with age leading to secondary hyperparathyroidism and bone resorption.[25] On the one hand, calcium and vitamin D supplementation can reduce the fracture risk in osteoporotic patients and is relatively cheap.[26] On the other hand, other anti-osteoporotic

therapies require optimal calcium and vitamin D levels[23] and necessitate adequate supplementation.

From large scale studies, it is clear that antiresorptive (e.g. bisphosphonates) and / or anabolic therapies (strontiumranelate, teriparatide) reduce the fracture risk in postmenopausal women with osteoporosis[27] and reduce the fracture risk and risk of death as well in previous hip fracture patients.[28]

However, long term compliance to drug therapy is low, especially in patients without preceding fracture[29] and with advancing age.[23]

Only a few research initiatives focus on the possible role of the surgeon treating fragility fractures in the post-operative management of the underlying osteoporosis, although the first results are promising.[30, 31] It is clear that the presence of treatment algorithms can be extremely useful.[31,32]

6. Influence of osteoporosis on the surgical treatment of fragility hip fractures and the possible role of augmentation

In the surgical treatment of osteoporotic hip fractures, two major types of treatment can be distinguished based on the fracture type: displaced intracapsular fractures are mostly treated by prosthetic replacement and undisplaced intracapsular fractures as well as all types of extracapsular fractures are treated by osteosynthesis.[33-35]

During the last decades, an evolution in the use of the type of implants for the treatment of extracapsular or intertrochanteric fractures has been noticed. Figure 3 illustrates the two main types of implants that are most frequently used. Figure 3a shows an intertrochanteric fracture treated with an extramedullary implant: the Dynamic Hip Screw (DHS). Figure 3b shows an intertrochanteric fracture treated with an intramedullary implant: the Proximal Femoral Nail Antirotation (PFNA).

Although there is no evidence that the use of intramedullary implants for the treatment of intertrochanteric hip fractures leads to a better outcome[35], there is a trend towards the use of nails.[36] A Cochrane review on the comparison of sliding hip screws versus intramedullary implants for the treatment of intertrochanteric fractures also suggests further research on new designs of intramedullary nails aimed to reduce perioperative fractures.[35]

Figure 3a

Figure 3b

Besides the biomechanical advantages of nailing for the treatment of hip fractures[37], other advantages are: the possibility to use minimal invasive techniques with only limited soft tissue damage, a rapid recovery and immediate full weight bearing.[38]
Within the intramedullary nailing group, there is no evidence that one type of nail is superior to another.[39] Several biomechanical studies however support the use of nails with blades over nails with standard cephalic screws.[40,41] Figure 3b is an illustration of a nail with a helical blade to fix the proximal fracture fragment. Despite the fact that more and more clinical studies support this finding as well[42-44], failures do still occur. Cut-out, a devastating complication of perforation of the femoral head by the cephalic screw or blade and secondary varisation of the femoral head, can be surgeon or bone related. In the first case, an incomplete fracture reduction of an unstable fracture or a suboptimal implant positioning can be noticed.[42,45,46] If this is not the case, it was found that cut-out is strongly related to the density of the trabecular bone in the femoral head.[47,48] Although the fracture healing potential of osteoporotic bone is normal, nonunions or malunions might occur due to implant loosening prior to the completion of the fracture healing process.[49] The problem of implant loosening before fracture healing in a well-reduced fracture, is illustrated in figure 4. Figure 4a shows an unstable intertrochanteric fracture in a 80 years old

lady. Figure 4b shows the postoperative radiograph: the fracture has been treated with an intramedullary nail after closed reduction on a fracture table. Figure 4c and 4d respectively show the anteroposterior and lateral views of the fracture one month postoperatively as a cut-out has occurred: migration of the cephalic screw through the femoral head followed by secondary varisation of the proximal fracture fragment.

Figure 4a

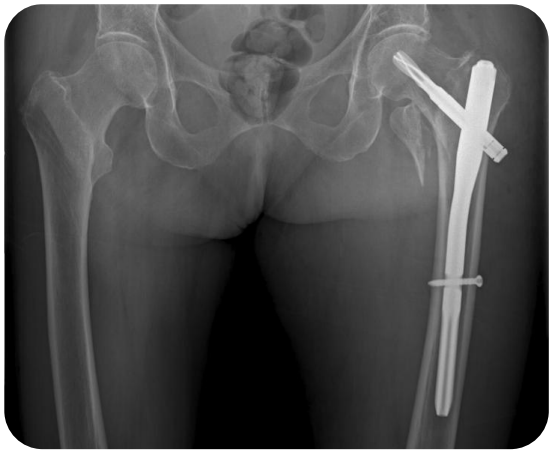

Figure 4b

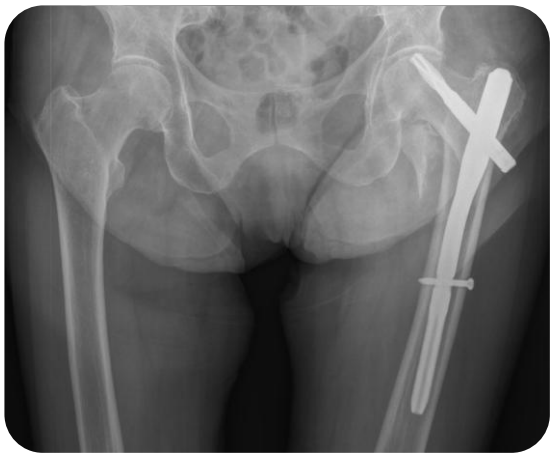

Figure 4c

Figure 4d

Due to the frail constitution of most of the osteoporotic hip fracture patients and due to the devastating consequences of revision surgery for these patients, it is of utmost importance to prevent mechanical complications and to go for a "one shot surgery".
In the past, augmentation of hip implants with bone cement has been used to prevent these kinds of problems. Cement augmentation has been very useful by increasing the strength of the implant fixation, by rapid restoration of the patient’s mobility and

by fewer complications due to implant failures.[49] The principle of implant augmentation is based on increasing the implant to bone interface by the addition of bone cement, reducing the stresses on the trabecular structures. Polymethylmethacrylate (PMMA) augmentation has been used as a solution to treat unstable trochanteric fractures by adding an anchoring ability to the lag screw, especially in osteoporotic bone.[50] This concept has been proven in numerous biomechanical and clinical studies.[51-54]

However, a lot of disadvantages have been attributed to cement augmentation. Most of them are related to the use of excessive amounts of PMMA. Primarily, impaired fracture healing has been mentioned as a consequence of cement leakage at the fracture site. This might lead to delayed or non-unions.[49,55-58] Secondly, there have been some concerns about thermal necrosis of the trabecular bone and the overlying cartilage of the femoral head caused by the exothermic reaction of the PMMA polymerisation.[49,56] Finally, there have been some concerns about implant removal in case of revision surgery which might be difficult due to the PMMA present in the femoral head. As absorbable cements are non-toxic and are replaced by host-bone over time, their use can overcome the above-described disadvantages related to the use of PMMA. Several authors report the successful use of degradable calcium phosphate cements in the treatment of intertrochanteric hip fractures in experimental and in clinical settings as well.[59-61] Nevertheless, the mechanical properties of absorbable cements are inferior compared to PMMA[62] and their use in osteoporotic bone should be questioned as they should be replaced by host bone over time.

In summary, the following two important problems actually are associated to fragility hip fracture treatment: the occurrence of secondary fractures and the mechanical failure of fixation due to the underlying osteoporotic bone. It is the aim of the current research project to focus on both of these problems resulting from important gaps in our current knowledge on the prevention and the treatment of fragility hip fractures and this from a surgical point of view.

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Objectives of the research

The aim of the current doctoral research program is to address the following priorities resulting from important gaps in our current knowledge on the prevention and the treatment of fragility hip fractures:

First of all, there is the clinical requirement to implement integrated referral pathways that will improve secondary fracture prevention. While it is clear that surgeons play a pivotal role in managing fracture patients, few research initiatives attempted to optimize post-fracture osteoporosis management by a surgeon-driven team.

Our second objective will be to investigate the benefits of new implant designs and fixation methods in preventing implant failure in osteoporotic bone. This will be done by a number of biomechanical experiments.

According to these priorities, a dual hypothesis will be addressed:

1) Systematic secondary fracture prevention in the context of a traumatologic-geriatric fracture prevention program will improve clinical outcome by reducing the fracture recurrence rate.
2) Optimizing existing osteosynthesis methods to fix proximal osteoporotic femoral fractures will reduce the complication rate by improving the implant fixation in the femoral head.

In line with both hypotheses, the objectives of the research project can be classified along two major research arms:

1) The development and testing of an integrated secondary fracture prevention program. This includes a meta-analysis of the long-term effects of clinical pathways for older hip fracture patients (**Chapter I**) and the development, the implementation and the evaluation of a traumatologic-geriatric fracture prevention program (**Chapter II**). This program will focus on older patients with recent hip fracture and will include the development of a multidisciplinary pathway for the systematic referral of hip-fracture patients from the traumatology department to a geriatric assessment unit for evaluation and treatment of osteoporosis, a comprehensive geriatric assessment, fall evaluation and fall prevention. As this will be a 'surgeon-driven' referral, it is the aim of the program to increase compliance to osteoporosis treatment. The evaluation of the program will include the assessment of its clinical impact.

2) The development and the implementation of new surgical techniques to improve implant fixation in the osteoporotic femoral head by biomechanically testing new surgical techniques. First of all, the concept of the technique of implant augmentation will be biomechanically tested on a foam model (**Chapter III**). Secondly, the feasibility of the surgical technique will be tested on a cadaver model followed by biomechanical testing (**Chapter IV**). Finally, after clinical implementation of the technique and preliminary feedback, a study on cement localisation will be performed on a foam model (**Chapter V**).

This research project will build on the existing research expertise of the Leuven University Center for Metabolic Bone Diseases (CMBD) in Leuven, Belgium, and the AO (Arbeitsgemeinschaft für Osteosynthesefragen) Research Institute in Davos, Switzerland.

Chapter I

The impact of care pathways for fragility hip fracture treatment on one-year mortality: systematic literature review and meta-analysis

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This chapter is in preparation for publication:

Sermon A, Herteleer M, Milisen K, Fieuws S, Vanhaecht K, Broos P, Richards R, Flamaing J. The impact of care pathways for fragility hip fracture treatment on one-year mortality: systematic literature review and meta-analysis.

1. Abstract

Background: Due to the increasing incidence of osteoporotic hip fractures, organizational improvement efforts are numerous. This evolution has lead to the development of clinical pathways for geriatric hip fracture treatment on the one hand and to the emergence of different types of co-managed care on the other hand. Besides a huge variety within the content of these programs, only short-term effects have been studied so far. It is the aim of the actual study to perform a systematic review of the literature on the long-term effects of clinical pathways for fragility hip fracture patients.

Materials and methods: A systematic search of the Medline, Embase, CINAHL and the Cochrane Database was performed from 1995 until present. Two independent reviewers screened all articles on clearly defined inclusion and exclusion criteria for clinical pathways for fragility hip fracture patients. The one-year mortality rate was set as primary outcome parameter, the prescription of anti-osteoporosis medication and the effect of care pathways on recurrent fracture rate were set as secondary outcome parameters.

Results: The literature search resulted in the selection of 11 studies of which four were randomized controlled trials and seven were non-randomized studies. A significant effect of clinical pathways for fragility hip fracture treatment on one-year mortality was found for non-randomized clinical trials and a positive but no significant effect was found for randomized controlled studies.
In only two of the included studies compliance to osteoporosis treatment was incorporated as an outcome parameter and none of the included studies reported recurrent fracture rate.

Conclusion: A positive effect on the one-year mortality could be observed for non-randomized studies on care pathways for fragility hip fracture treatment. Although a similar effect could be observed for the randomized studies, formal evidence is lacking. Furthermore, no data about recurrence fracture rate and only very limited data on medical osteoporosis treatment could be found in the included studies.

2. Introduction

During the last decades, big advances have been made in the organization of the care for fragility hip fracture patients. This is probably due to the increasing incidence of osteoporotic hip fractures and their devastating consequences for the individual patients and for society in general. Fragility hip fracture patients have a 5- to 8-fold increased risk of death in the three to six months following their fracture. It has been shown that this excess mortality persists over time and this for both women and men. It is not clear whether osteoporotic hip fracture patients suffer more from underlying frailty or whether the hip fracture on itself acts like a trigger inducing frailty.[1] As our active aging population will continue to grow, the incidence of osteoporotic hip fractures and the economic consequences will do likewise. In Europe, there was an incidence of 3.5 million osteoporotic fractures generating an economic burden of € 37 billion in 2010. It was calculated that these costs will increase with 25% in 2025.[2]

These striking numbers lead to organizational improvement efforts in the care for fragility hip fracture patients. On the one hand, clinical pathways for geriatric hip fracture patients have been developed. Following the definition of Vanhaecht et al[3], a clinical pathway is "a complex intervention for mutual decision making and organization of predictable care for a well-defined group of patients during a well-defined period". Following the definition of Rotter et al[4], clinical pathways are focusing on a specific patient population, bringing evidence to practice and trying to optimize clinical outcomes by a multidisciplinary team approach.

On the other hand, the so-called co-managed care has become familiar to most trauma and orthopaedic surgeons. In a literature review, four types of co-managed care could be distinguished: an orthopaedic ward with geriatric consultant service on demand, an orthopaedic ward with a daily geriatric consultative service, a geriatric and rehabilitation ward with orthopaedic consultant service and an orthopaedic ward with integrated geriatric care.[5] When studying these different types of co-managed care in detail, it becomes clear that the four models correspond more or less to the definition of a clinical pathway but that the fourth model "orthopaedic ward and integrated geriatric care" corresponds the best.

The effects of co-managed care and of clinical pathways for fragility hip fracture treatment have been studied extensively. In a meta-analysis on clinical pathways for hip fracture patients, a significant influence on in-hospital complications like deep

venous thrombosis, pressure ulcer, surgical site infection and urinary tract infection was found while no significant influence on short term mortality could be documented.[6] Clinical pathways tend to document and decrease in-hospital complications without influencing the length of stay.[4] In a meta-analysis on orthogeriatric care models, it was concluded that orthogeriatric collaboration leads to a better in-hospital and long-term mortality as well.[7] A weakness of this meta-analysis however is the inclusion of three different types of orthogeriatric care, leading to heterogeneity. Only the “shared care” model, where both the geriatrician and the surgeon share the responsibility for the care of the patient, can be classified as a clinical pathway strictu sensu.

Furthermore, most studies on clinical pathways for fragility hip fracture treatment only focus on short-term effects like length of stay and in-hospital or 30-day mortality. Only scarce and heterogeneous information is available on long-term mortality. However, in a review of the literature completed by a multidisciplinary meeting, orthopaedic surgeons, trauma surgeons and geriatricians from Europe, USA and Canada tried to generate consensus on which outcome parameters to use for the evaluation of orthogeriatric co-management. Long-term mortality was withheld as outcome parameter to be measured until one year after admission as was the medical treatment of the underlying osteoporosis.[8]

Both primary (before the hip fracture) and secondary (after the hip fracture) decrease of bone mineral density (BMD) are associated with an increased mortality.[9-11] The prescription and administration of anti-osteoporosis medication following a fragility fracture, should be included in the discharge planning as part of the comanaged care for fragility hip fracture patients.

It is the aim of this systematic review to perform an extensive review of the available literature on the subject. The primary research question will be to evaluate the effect of clinical pathways for fragility hip fracture treatment on the 6 months and 1 year mortality. The secondary research questions will be to evaluate the post-fracture prescription of anti-osteoporosis medication and the effect of clinical pathways on recurrent fracture rate. Only primary studies on clinical pathways fulfilling the definition of Vanhaecht et al.[3] will be included but secondary studies will be hand-searched for relevant references.

3. Materials and methods

3.1. Data sources and searches

A systematic search of the following databases was performed: Medline, Embase, CINAHL and The Cochrane Library. All databases were explored from 1995 until present.

The following search terms were used: "hip fractures" (Medical Subject Heading (MeSH)), or "subtrochanteric fracture", or "trochanteric fracture", or "intertrochanteric fracture", or "broken hip", or "osteoporotic fractures" (MeSH), AND "critical pathways" (MeSH), or "clinical pathway", or "referral pathway", or "care" and "pathway", or "referral and consultation", or "secondary care" (MeSH), or "orthogeriatric" and "team" and "work" (MeSH), or "geriatric assessment" (MeSH), or "orthogeriatric" and "comanagement", or "orthogeriatric" and "organization" and "administration" (MeSH), or "management", or "disease management" (MeSH), or "patient care team" (MeSH), or "interdisciplinary health teams", AND "mortality" (MeSH), or "death rate", or "death rate constant", or "mortality decline", or "fatality rate", or "hospital mortality" (MeSH), or "survival rate" (MeSH), or "survival time", or "epidemiology", or "morbidity" (MeSH), or "patient readmission" (MeSH), or "reintervention", or "reinterventional", or "comorbidity" (MeSH).

3.2. Inclusion and exclusion criteria

Only primary literature (randomized controlled trials and non-randomized studies) was included. The selected literature had to be in English and had to involve co-managed care for geriatric hip fracture patients corresponding to the definition of a clinical pathway (also termed a critical pathway, care path, or care map) of Vanhaecht et al.[3] The main features of clinical pathways are the implementation of evidence based key interventions by a multidisciplinary team approach and the active follow-up of the process. A control group had to be included in the study and should consist out of geriatric hip fracture patients treated without co-managed care. The included studies had to provide information on the 6 months or one-year mortality and were subsequently checked for medical osteoporosis treatment or fracture recurrence rate within the first year following the fracture.

Studies were excluded if they met another research design or covered a different setting. Articles were excluded if they were published before 1995 or if they included

patients younger than 60. We decided not to include secondary literature (review articles and meta-analyses) but references of all included studies and of secondary studies were hand-searched for additional publications.

3.3. Study selection

One reviewer (H.M.) screened all titles and keywords of the retrieved studies to assess their eligibility according to the above-mentioned inclusion and exclusion criteria. Articles that did not meet the inclusion criteria were excluded during this phase. The abstracts of the remaining articles were subsequently screened by two reviewers (H.M. & S.A.). Studies were excluded if the abstract did not meet the inclusion criteria. Of the remaining studies, the full text articles were examined by both reviewers. Studies not dealing with a clinical pathway on geriatric hip fracture treatment, were excluded. Disagreements were resolved by discussion until consensus was obtained.

3.4. Methodological quality assessment

To assess the methodological quality of the included non-randomized studies, the Newcastle-Ottawa scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)[12] was used. A maximum of 9 stars could be provided to each study, evaluating patient selection, comparability of study groups and assessment of outcome.

The results are shown in Table 1. A maximum of 9 stars could be afforded to each study, evaluating patient selection (4 items, maximum of 4 stars), comparability of study groups (2 items, maximum of 2 stars) and assessment of outcome (3 items, maximum of 3 stars).

Study	Selection	Comparability	Outcome	Stars (total)
Barone (14)	**	*	**	5
Cogan (20)	***	**	**	7
Leung (21)	****	*	**	7
Koval (22)	****	**	**	8
Wagner (23)	****	-	**	6
Dy (24)	**	-	**	4
Adunsky (25)	****	-	**	6

Table 1: Quality assessment of non-randomized studies using the Newcastle-Ottawa scale

3.5. Care pathway evaluation

The full text of all possibly relevant articles was checked for the definition of a clinical pathway, using the criteria of Vanhaecht et al.[3] Primarily, at least two or more evidence-based key interventions concerning the pre-operative, intra-operative or postoperative care had to be included. Secondly, a multidisciplinary team approach had to be present with shared responsibility for the osteoporotic hip fracture patients by surgeons and geriatricians, so all models based on consultancy were excluded. Finally, an evaluation of the pathway had to be performed by the presence of a control group. If an article fulfilled all of the above mentioned criteria, it was included in the meta-analysis, even if it was not literally called a clinical pathway.

3.6. Data extraction and statistical analysis

The following data were extracted from each study: study design, time of follow-up, number of included patients at start of the study, number of included patients at 6 months, number/percentage of deceased patients at 6 months, number of included patients at 12 months, number/percentage of deceased patients at 12 months, number/percentage of fracture recurrences at 12 months, and medical osteoporosis treatment prescribed at discharge: type of medication and number of patients discharged with a prescription.

Odds ratios comparing the 12-month mortality have been reported for the various studies. Depending on the study, the reported 12-month mortality referred to crude numbers (numerator and denominator), a crude percentage or a percentage derived from a Kaplan-Meier curve. As the 12-month mortality referred to crude numbers, a crude percentage or a percentage derived from a Kaplan-Meier curve, the analysis as such is a simplification since drop-out is not taken into account. For the Kaplan-Meier estimates, the information on the actual risk set is missing. For studies reporting crude numbers or percentages, the number of patients at inclusion is used as denominator. In case no data were available for the 12-month mortality, the 6-month mortality has been used; this was done for 1 study.[13] Further, for the study of Barone et al.[14], both control groups (before and after) were combined into one group.

A meta-analysis has been performed separately for non-randomized and randomized studies. Observed differences in effect size between the studies reflect true variability (between-study variability or heterogeneity) and sampling variability (within-study variability).

Heterogeneity was quantified by the I^2 statistic[15] which is the percentage of total variation in study estimates that is due to heterogeneity and tested by Cochran's X^2-test. The random-effects approach of DerSimonian and Laird[16] was used to obtain a pooled estimate as a weighted average of the study-specific estimates.

4. Results

4.1. Study selection

The results of the search strategy are summarized as a flowchart in figure 1.

The preliminary search resulted in 1,479 citations of which 233 were eliminated as duplicates. Of the 1,246 remaining studies, 1,203 were excluded after title and / or abstract screening based on the in- and exclusion criteria. The 43 remaining studies were considered for full text reading. 32 studies were excluded because they did not answer to the definition of a clinical pathway. Finally, 11 studies were retained for statistical analysis, of which four were randomized controlled studies[13,17-19] and seven non-randomized studies.[14, 20-25]

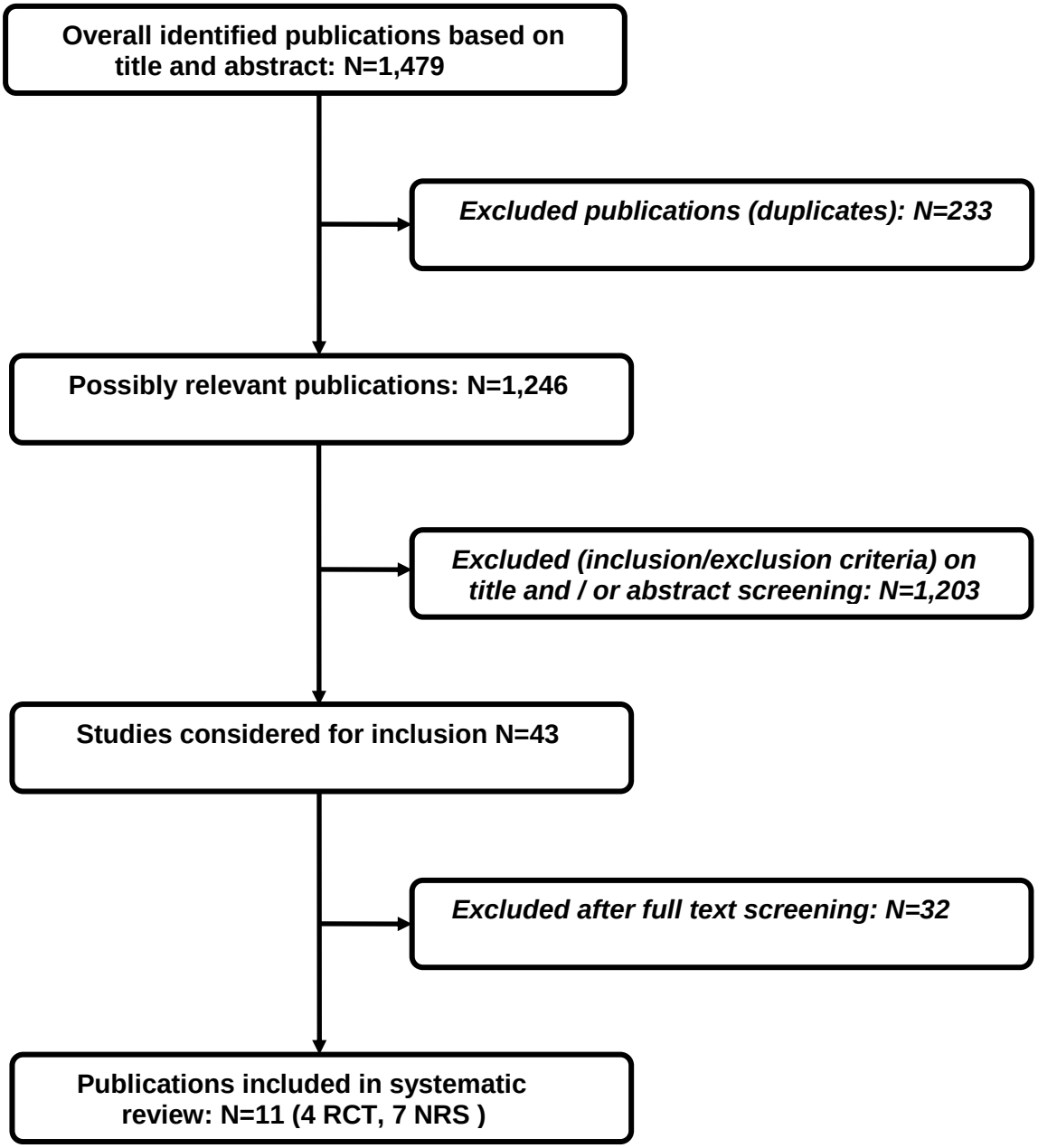

Figure 1: Study selection

(RCT = Randomized Controlled Trial, NRS = Non-Randomized Study)

4.2. Descriptive information

The descriptive information on outcome of the included studies is summarized in Table 2. Of the 11 included studies, four were randomized controlled trials[13,17-19] and seven were non-randomized studies.[14,20-25] The follow-up time of all studies was 12 months, except for the study of Naglie et al.[13] with a follow-up time of 6 months. All studies reported on mortality. Only two studies reported on osteoporosis treatment[20,23] and in none of the studies recurrent fractures were mentioned.

Study	SD	FUTime	N1	Ndeath1	%death1	N0	Ndeath0	%death0	OstMed	%med1	%med0	Nrecur1	Nrecur0
Barone[14]	NRS	12	252		25.0	567		34.3					
Cogan[20]	NRS	12	98		34.0	103		45.0	Bisph Ca	54 60	1 2		
Leung[21]	NRS	12	278	32		270	55						
Koval[22]	NRS	12	747	66		318	45						
Wagner[23]	NRS	12	92		13.0	183		13.0	Ca + vit D	100	5		
Dy[24]	NRS	12	34	9		40	9						
Adunsky[25]	NRS	12	847		14.8	2,267		17.3					
Vidan[17]	RCT	12	155		18.9	164		25.3					
Day[18]	RCT	12	38		8.0	33		13.0					
Shyu[19]	RCT	12	79	4		80	6						
Naglie[13]	RCT	6	141	17		138	21						

Table 2: Descriptive information of the included studies

(SD = study design (NRS = non-randomized study, RCT = randomized controlled trial); FUTime = follow-up time in months; N1 = number of included patients in the intervention group; Ndeath1 = number of deceased patients in the intervention group at the end of the study; %death1 = percentage of deceased patients in the intervention group at the end of study; N0 = number of included patients in the control group; Ndeath0 = number of deceased patients in the control group at the end of the study; %death0 = percentage of deceased patients in the control group at the end of study; OstMed = type of anti-osteoporosis medication provided to the included patients (Bisph = Bisphosphonate, Ca = calcium, vit D = vitamin D); %med1 = percentage of patients receiving medical osteoporosis treatment in the intervention group; %med0 = percentage of patients receiving medical osteoporosis treatment in the control group; Nrecurr1 = number of recurrent fractures in the intervention group at the end of the study; Nrecur0 = number of recurrent fractures in the control group at the end of the study)

4.3. Mortality

The results are summarized in Table 3 and Figure 2 for the non-randomized studies and in Table 4 and Figure 3 for the randomized studies. Odds ratios (intervention versus control) comparing the 12-month mortality have been reported for the various studies. The meta-analysis of the non-randomized studies (Figure 2 and Table 3) shows a significant difference in mortality at 12 months in favour of the intervention group.

The meta-analysis of the randomized studies (Figure 3 and Table 4) shows also a difference in mortality at 12 months in favour of the intervention group, although non significant. For the non-randomized studies, there was a non significant between-study heterogeneity (I^2 = 15.2%, Cochran's Q = 7.08, df = 6, p = 0.3137). For the randomized studies, there was no between-study heterogeneity (I^2 = 0.0%, Cochran's Q = 0.09, df = 3, p = 0.9926).

4.4. Osteoporosis treatment

Only in two studies[20,23] information was provided about the prescription of medical osteoporosis treatment at discharge. In the study of Cogan et al.[20], 54% of the patients in the intervention group received a prescription for bisphosphonates at discharge compared to 1% of the patients in the control group. 60% of the patients in the intervention group received a co-prescription for calcium compared to 2% in the control group. In the study of Wagner et al.[23], calcium and vitamin D was prescribed at discharge to 100% of patients in the intervention group compared to 5% in the control group. Because of the lacking of information about osteoporosis treatment in the other studies, no meta-analysis on this subject could be performed.

4.5. Recurrent fractures

In none of the included studies information was provided on recurrent fractures within the first year following the initial fracture. If information on readmissions was included at all, only medical reasons for readmissions were reported.

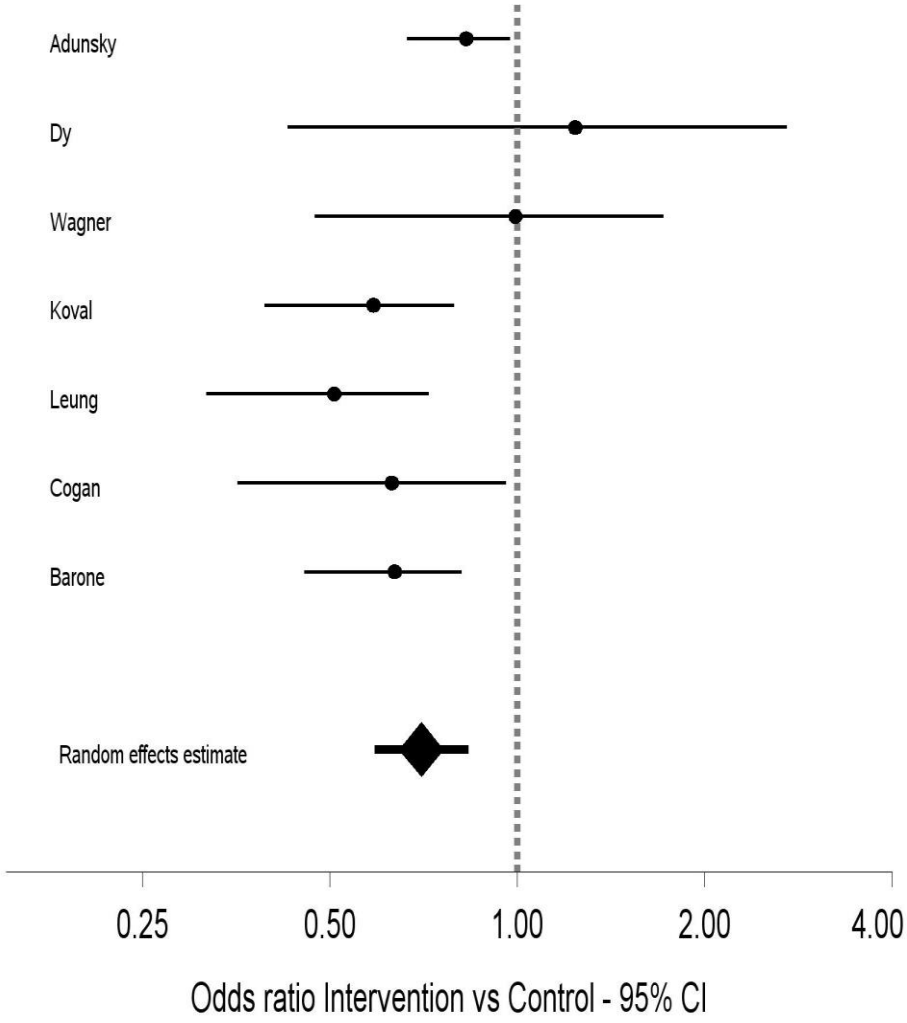

Figure 2: Odds ratios comparing 12-month mortality for the non-randomized studies. The combined effect size is given at the bottom of the figure.

	Intervention			Control			
Study	**N**	**N events**	**%**	**N**	**N events**	**%**	**Odds ratio (95%CI)**
Barone	252	63	25.0%	567	195	34.4%	0.636 (0.455;0.812)
Cogan	98	33	33.7%	103	46	44.7%	0.629 (0.355;0.957)
Leung	278	32	11.5%	270	55	20.4%	0.508 (0.317;0.720)
Koval	747	66	8.8%	318	45	14.2%	0.588 (0.393;0.791)
Wagner	92	12	13.0%	183	24	13.1%	0.994 (0.473;1.715)
Dy	34	9	26.5%	40	9	22.5%	1.240 (0.428;2.708)
Adunsky	847	125	14.8%	2267	392	17.3%	0.828 (0.665;0.973)
	.	.	.	.	.	.	
Meta-analyses:	.	.	.	.	.	.	
Fixed effects estimate	.	.	.	.	.	.	0.715 (0.617;0.828)
Random effects estimate	.	.	.	.	.	.	0.702 (0.591;0.833)

Evaluation between-study heterogeneity: I^2=15.2%, Q=7.08, df=6, p=0.3137
I^2=percentage of variation in study estimates due to heterogeneity. Q=Cochrans Q statistic.Df=Degrees of Freedom for heterogeneity test.
Random Effects Analysis: DerSimonian and Laird method.

Table 3: Odds ratios comparing 12-month mortality for the non-randomized studies.

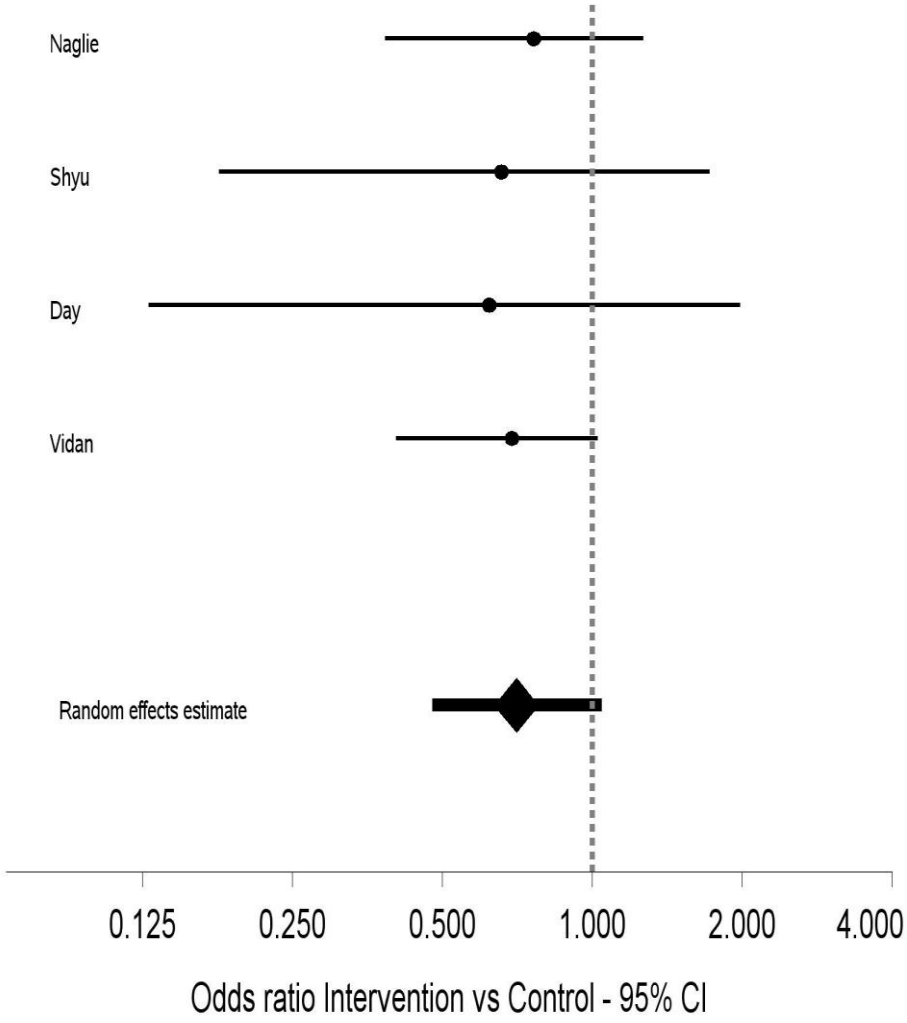

Figure 3: Odds ratios comparing 12-month mortality for the randomized studies. The combined effect size is given at the bottom of the figure.

	Intervention			Control			
Study	**N**	**N events**	**%**	**N**	**N events**	**%**	**Odds ratio (95%CI)**
Vidan	155	29	18.7%	164	41	25.0%	0.690 (0.404;1.024)
Day	38	3	7.9%	33	4	12.1%	0.621 (0.129;1.977)
Shyu	79	4	5.1%	80	6	7.5%	0.658 (0.178;1.716)
Naglie	141	17	12.1%	138	21	15.2%	0.764 (0.384;1.266)
	.	.	.	.	.	.	
Meta-analyses:	.	.	.	.	.	.	
Fixed effects estimate	.	.	.	.	.	.	0.706 (0.478;1.042)
Random effects estimate	.	.	.	.	.	.	0.706 (0.478;1.042)

Evaluation between-study heterogeneity: I^2=0.0%, Q=0.09, df=3, p=0.9926
I^2=percentage of variation in study estimates due to heterogeneity. Q=Cochrans Q statistic.Df=Degrees of Freedom for heterogeneity test.
Random Effects Analysis: DerSimonian and Laird method.

Table 4: Odds ratios comparing 12-month mortality for the randomized studies

5. Discussion

5.1. Methodological considerations

The literature search resulted in the selection of 11 studies of which four were randomized controlled trials and seven were non-randomized studies. Because of this small number of studies retrieved, it was decided to include all the withheld studies in the review but performing a separate meta-analysis for the randomized and non-randomized studies as non-randomized studies include a bigger risk of bias.

A possible explanation for the absence of randomized controlled studies on the subject could be the existing evidence of the studied intervention.[26] As there is evidence about the short term advantages (e.g. in-hospital mortality, pressure sores, surgical site infections, medical complications) of clinical pathways for fragility hip fracture treatment[6,27] and of orthogeriatric care models[7], it would be non ethical to exclude a patient group from this intervention by performing randomized controlled trials evaluating long-term effects. Another explanation especially for the missing data on long-term mortality in general, could be the difficulty of long-term follow-up of a geriatric patient population. Despite the inclusion of non-randomized studies in a separate meta-analysis however, heterogeneity between these studies was low as was quantified by the I^2 statistics of Higgins and Thompson.[15]

As non-randomized studies contain a larger risk for bias, a methodological quality check was performed on the seven included non-randomized studies by using the Newcastle-Ottawa scale.[12] As summarized in Table 1, selection bias was rather low for most studies as was reporting bias (evaluated as "outcome"). Comparability however was difficult to assess because no information on comparability of study cohorts was provided in three of the seven included studies.[23-25] On the other hand because the effect size of the meta-analysis was measured as odds ratio and not as relative risk, the influence of possible differences in study populations between studies was ruled out presuming that intervention and control groups within each study are comparable.

5.2. Considerations on the structure and the content of the clinical pathways of the included studies

Concerning the structure of the clinical pathways included in this literature study, strong selection criteria were used. These selection criteria give our analysis an added value compared to previously performed literature studies including different types of interventions, making pooling of the results much more difficult. Studies could only be included in our analysis if the described pathway comprised two or more evidence based key-interventions, if a multidisciplinary team approach was used and if there was an active follow-up of the process. By doing this, only evidence-based, multidisciplinary and controlled processes were included, allowing us to pool the results, independently from the name given to the pathway or care process. The analysis of the included studies indeed revealed a huge diversity in names given to the interventions: four studies mentioned “orthogeriatric service”[14,20,21,23], three studies talked about “multi- or interdisciplinary care”[17,19,13], three studies used a unique name: “comanaged care”[24], “liaison team”[18], "comprehensive geriatric hip fracture unit"[25] and only in one study the intervention was called a “clinical pathway”.[22]

By the use of clear selection criteria however, it became clear that the content of the interventions is more important than the name given to it. Consequently, it was not necessary for a study to be called a "clinical pathway" to be included in this meta-analysis.

Concerning the content of the clinical pathways, a big variability could be observed. At first sight, this finding could make it more difficult to draw any conclusion. A detailed analysis of the reported key-interventions however, enabled us to sort all interventions in one of the following three groups: inpatient care with special attention to medical comorbidities (preoperatively, peroperatively and postoperatively), rehabilitation and discharge planning.

5.3. Considerations on the effects of clinical pathways

This study revealed a significant effect of clinical pathways for fragility hip fracture treatment on the long-term mortality for non-randomized studies only. For the randomized controlled trials included in the study however, a positive but not significant effect could be found on the 1-year mortality. This is a new finding besides the already known short term effects on length of stay and in-hospital complications.[6,27] This should encourage any surgeon treating osteoporotic hip fracture patients to go for well-organized, interdisciplinary care for this frail patient population. Before, the beneficial effects of multidisciplinary and organized care for geriatric patients have only been proven on dedicated geriatric wards and Geriatric Assessment and Management Units (GEMU). A Cochrane review could show a significant increase in survival after one year if comprehensive geriatric assessment was provided on a dedicated geriatric ward[28]. A meta-analysis on the effects of GEMU could show significant effects on functional decline at discharge and on institutionalization after one year in favour of GEMU compared to usual care. No significant effect could be shown on mortality at any specific time point.[29]

None of the included studies mentioned recurrent fractures. In literature however, very high numbers of recurrent osteoporotic hip fractures can be found: the 10-year probability of a recurrent hip fracture after a primary osteoporotic hip fracture reaches nearly 25%.[30,31] Furthermore, patients with recurrent osteoporotic fractures not only suffer from the morbidity associated to the secondary fracture, but they also experience an associated high mortality.[31]

Finally, only in two studies medical osteoporosis treatment was mentioned. The effectiveness however of anti-resorptive therapy on the prevention of recurrent hip fractures as well as on the mortality in general, has been proven.[32,33] Despite this finding, the long-term compliance to anti-osteoporosis treatment is low[34,35], as is confirmed in a study on the Belgian situation.[34]

The positive effect of clinical pathways for fragility hip fracture treatment on in-hospital complications and on both short- and long-term mortality, should encourage surgeons to start medical osteoporosis treatment after a first fragility fracture. In the light of the multidisciplinary care and follow-up of the patients, any treating physician should encourage long-term compliance to this treatment.

5.4. Limitations of the actual study and considerations for further research

The actual review of the literature and meta-analyses have several limitations.

First of all, only a small number of studies could be found. The study design of these studies (four randomized controlled trials and seven non-randomized studies) forced us to perform two separate meta-analyses. Only for the non-randomized studies, a significant effect of clinical pathways on one-year mortality could be shown whereas a positive although non-significant effect could be shown for the randomized controlled studies. As only four randomized controlled studies could be included and the total number of patients included in the randomized controlled studies is much lower (828 versus 6096 in the non-randomized studies), formal evidence is lacking for the randomized studies although a similar positive effect of care pathways could be observed on the one-year mortality. Furthermore, no data about recurrence fracture rate and only very limited data on medical osteoporosis treatment could be found in the included studies. Further research on this subject is needed: at first to rule out if this is a reporting problem or really a missed chance for secondary fracture prevention. In any way, attention should be given to include refracture prevention in clinical pathways for geriatric hip fracture treatment.

6. Conclusion

A meta-analysis performed on clinical pathways for fragility hip fracture treatment showed a significant effect on 1 year mortality for non-randomized clinical trials and a positive as well but non significant effect for randomized controlled studies.

In only two of the included studies compliance to osteoporosis treatment was incorporated as an outcome parameter and none of the included studies reported recurrent fracture rate.

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Chapter II

The impact of a traumatologic-geriatric post-fracture program for osteoporotic hip fracture patients

This chapter is in preparation for publication:
Sermon A, Boonen S, Michiels T, Broos P, Richards R, Flamaing J. The impact of a traumatologic-geriatric post-fracture program for osteoporotic hip fracture patients.

1. Abstract

Objectives: To assess the impact of a traumatologic-geriatric fracture prevention program on process and outcome parameters in osteoporotic hip fracture patients.

Setting: Department of Traumatology and Center for Metabolic Bone Diseases, University Hospitals Gasthuisberg, Leuven, Belgium.

Design: Retrospective study performed by patient chart analysis. The included patients are all 65 years of age or older and were admitted to the Department of Traumatology with an osteoporotic hip fracture. The traumatologic-geriatric hip fracture program consisted of administration of calcium and vitamin D supplements and referral to the Center for Metabolic Bone Diseases to assess the osteoporosis risk and to administer bisphosphonates if indicated. Furthermore, patients, their family and general practitioners were informed about the importance of osteoporosis. Two groups were created: an intervention group of patients subjected to the program (n=193) and a historical control group treated by standard care (n=253). Demographic, process and outcome parameters for both groups were compared.

Main Measurements: The following process indicators were studied: administration of calcium, vitamin D and bisphosphonates; information to patients, their relatives and general practitioners; referral to geriatric one day clinic or outpatient consultation. Furthermore the following outcome parameters were studied: time until new fracture and mortality within the first year.

Results: While comparing both groups, statistic significant differences for all process indicators were observed. However, no statistically significant changes in main outcome measurements were observed.

Conclusions: In this study, a traumatologic-geriatric post-fracture program aiming at the prevention of osteoporotic recurrent fractures in geriatric hip fracture patients was not associated with a significant reduction in fracture recurrence and mortality within the first year after the fracture. Nevertheless, a significant difference was observed between the two study groups for all process indicators. How to organize a post-hip

fracture program with an impact on fracture recurrence and mortality, needs further investigation.

2. Introduction

During the last decades, a worldwide increase in osteoporosis related hip fractures has been noticed.[1] For the European Union, there is a yearly incidence of about 620,000 hip fractures in women and men. In Belgium, the yearly incidence is about 15,000.[2] Due to the aging of our population and to the higher activity level of the older persons, a further increase of the number of hip fractures is expected.[3]

Besides a tremendous increase in health care related costs, the consequences of hip fractures for the individual patients are devastating.[4] There is a significant decline in the ability to perform activities of daily living for most of the patients and up to 10 to 20% of hip fracture patients are not able to return to their previous residence and need some form of assisted care. Furthermore, the mortality rate in the year following a hip fracture rises to 30%.[5] Moreover, recent studies show that this excess mortality persists over time for both women and men: the risk of death in the 10 to 15 years following a hip fracture is 3 to 4 times as high as in the non-hip fracture patient population.[6,7] It has become clear that a hip fracture is a sign of frailty: hip fracture patients often suffer from underlying comorbidities resulting in a limited functionality and health prior to the fracture.[8] There is no doubt that the concomitant management of these comorbidities has an important influence on the outcome of elderly patients with hip fractures.[9] Due to the amelioration of the surgical techniques for treating hip fractures, good medical aftercare has become as important as good operative fracture treatment. Finally, next to medical complications, hip fracture patients suffer from an increased bone degradation with an inherent risk of recurrent fractures as well.[10]

During the last years, the beneficial effect of care pathways for fragility hip fracture treatment has become clear. As most of the orthogeriatric fracture care programs comprise a systematic approach of evidence-based key interventions in a multidisciplinary and controlled way, they can be called care pathways following the definition of Vanhaecht et al.[11] Most studies on care pathways however, prove their influence on short-term effects like in-hospital complications, length of stay and 30-days mortality.[12,13] In a recent systematic review of the literature and meta-analysis

(Chapter I) however, the beneficial effect of care pathways on the 1-year mortality could be demonstrated. On the other hand, no data about recurrence fracture rate and only very limited data on medical osteoporosis treatment could be found in the included studies. Too little attention has been given to secondary fracture prevention as 2-6 % of hip fractures are recurrent fractures.[7]

From large-scale studies, the beneficial effect of pharmacological prevention on recurrent hip fractures has become clear. In the "recurrent fracture trial", the authors could show a reduction in fracture risk as well as in mortality in a population of previous hip fracture patients by the once-yearly intravenous administration of zoledronic acid.[14] Despite existing guidelines on medical osteoporosis treatment[15,16] , implementation in clinical practice is suboptimal.[17] For the Belgian situation, it has been shown that only a minority of hip fracture patients take anti-resorptive medication after a fragility hip fracture. Of those who initiated treatment however, adherence diminishes over time and remains suboptimal.[18] This finding corresponds to previous studies, proving low compliance to anti-resorptive medication.[19,20]

The current study evaluates the introduction of a clinical pathway for medical osteoporosis treatment and prevention of recurrent fractures. In the Department of Traumatology of the University Hospitals Leuven, Belgium, a protocol-driven comanaged care for fragility hip fracture patients was implemented. This program is characterised by a multidisciplinary approach of the geriatric hip fracture patient from the moment of admission to discharge. The main objective is a successful treatment of the geriatric hip fracture patient by providing the best surgical fracture care as well as correct and timely treatment of the underlying comorbidities. With the development and the implementation of a traumatologic-geriatric post-fracture program, the treatment of the underlying osteoporosis was included in the care for the geriatric hip fracture patient. This care program consists of a surgeon-driven integrated pathway of clinical referral and care for osteoporotic hip-fracture patients. By a systematic referral of all fragility fracture patients to the Center for Metabolic Bone Diseases (CMBD) of the UZ Leuven, the underlying osteoporosis is evaluated and managed with pharmacological as well as non-pharmacological preventive measures. The objective of the program is to decrease the number of secondary osteoporotic fractures. The implementation of this post-fracture program was started in January 2010. This study compares the process and outcome parameters of

patients included in the traumatologic-geriatric post-fracture program with a historical study group.

3. Materials and methods

3.1. Introduction and implementation of clinical pathway

The clinical pathway "prevention of recurrent fractures after fragility hip fracture" was introduced in the Department of Traumatology of the University Hospitals Leuven from January 2010 on. The pathway was based on a collaboration of the Traumatology Department and the CMBD. The authors SB and AS developed the clinical pathway in consensus following the actual available evidence on the subject. The inclusion criteria are as follows: patients of 65 years of age or older who sustain a fragility hip fracture and who are able to come to the CMBD on an ambulatory base. The following exclusion criteria are used: patients who are younger than 65 years, who sustained a non-fragility fracture (e.g. pathologic fracture, polytrauma,...) or who are not able to come to the CMBD on an ambulatory base. Patients are included in the pathway as soon as they are hospitalized on the traumatology department for the treatment of a fragility hip fracture.

The following key interventions are performed after inclusion in the pathway:

- The administration of calcium (1000 mg) and vitamin D (800 IU (International Units)).
- The systematic referral to the CMBD for the evaluation and treatment of underlying osteoporosis.
- Providing information about the clinical pathway to the patient, her / his family and general practitioner.

Figure 1 displays a flow-chart of the clinical pathway.

Patients under the age of 75 visit the outpatient clinic of the CMBD where the following interventions are performed: a comprehensive geriatric assessment and a DEXA (Dual Energy X-Ray Absorptiometry)-scan followed by pharmacological osteoporosis (when present) treatment and non-pharmacological fall prevention measurements.

Patients above 75 years receive the interventions of the CMBD through a visit of the geriatric day-hospital, as this constitutes a more comfortable setting adjusted to their age-related physical and mental restrictions.

Here a comprehensive geriatric assessment is performed and intravenous anti-osteoporosis therapy is administered if there are no contra-indications. A DEXA-scan is performed to determine the baseline-value of the underlying bone quality. Furthermore non-pharmacological fall prevention measurements are administered.

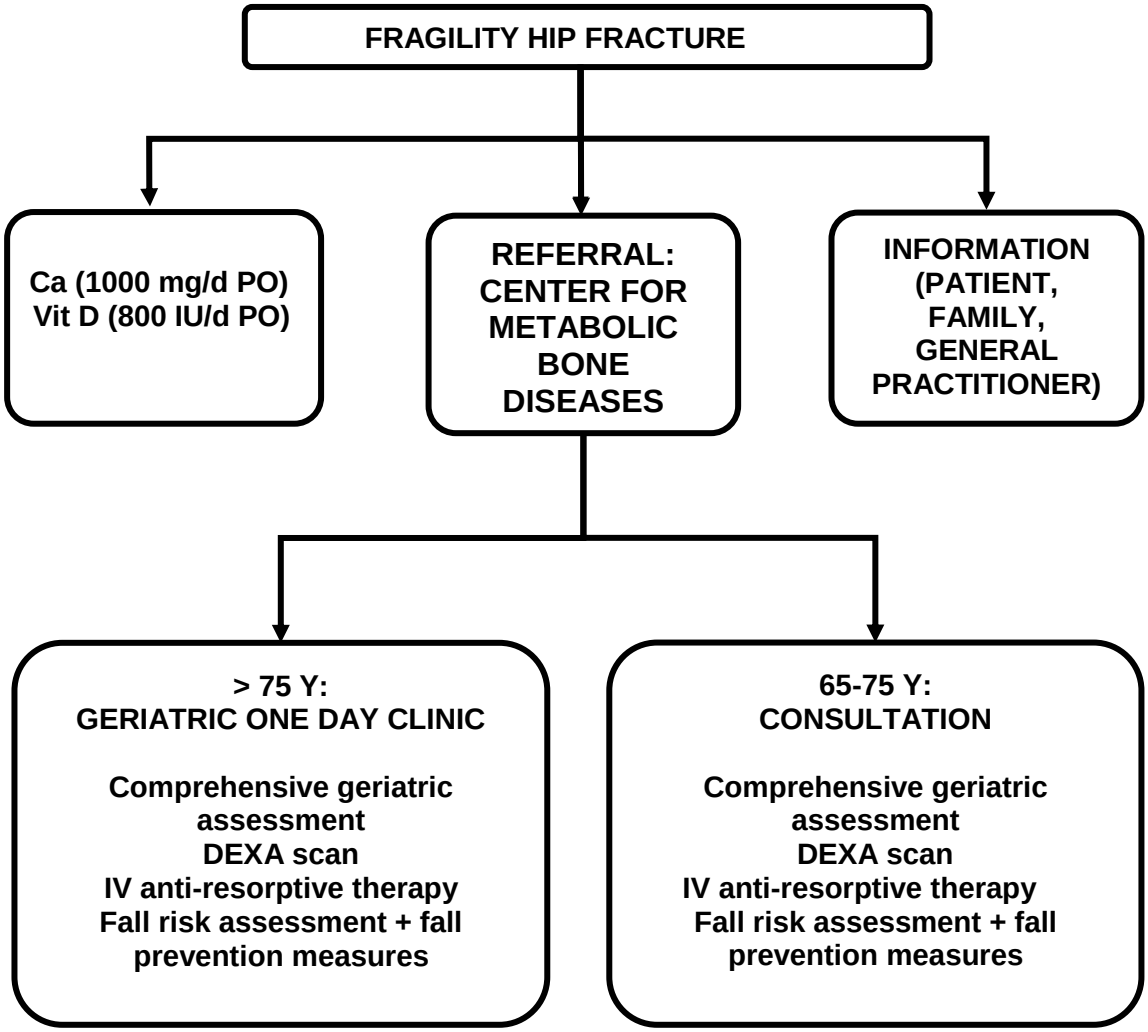


Figure 1: Flow-chart of clinical pathway

3.2. Evaluation of clinical pathway

To evaluate the clinical pathway, a retrospective study was performed by patient chart analysis. Two study groups were created: an intervention group of patients included in the clinical pathway (patients treated for a fragility hip fracture between April 1st, 2010 until September 30th, 2011; n=193) and a historical control group treated by standard care before the introduction of the clinical pathway (patients treated for a fragility hip fracture from April 1st, 2008 until September 30th 2009; n=253). Demographic, process and outcome parameters for both groups were compared. A retrospective review of patients' charts was performed with a standardized form to collect the required data from the day of the fracture to one year postoperatively. In those cases where the data could not be retrieved from the patients' charts, a document was sent to the patients, asking them to fill in the missing information. Data were collected on demographic characteristics (age and sex), comorbidities (ASA (American Society of Anaesthesiologists)-score), fracture type (fracture classification and preceding fractures), treatment type and duration of follow-up. Furthermore the following process indicators were collected: start of calcium and vitamin D administration during the hospital admission following the hip fracture, referral to the CMBD and information provided to the patient, his / her family and the general practitioner. Finally, the following outcome parameters were collected one year after sustaining the fracture: complications, readmissions, reinterventions, subsequent hip fracture, mortality. All data were handled anonymously. The study was approved by the Ethical Committee of the University Hospitals Gasthuisberg (study number S55746, Belgian number B322201318524).

3.3. Statistical analysis

Fisher's exact test was used to compare categorical and ordinal variables between groups and Mann-Whitney U test was used to compare continuous variables between groups. Curves for overall survival, time until readmission and time until a new fracture were constructed using Kaplan-Meier estimates and compared between groups with a log-rank test. Only events within one year were considered. P-values smaller than 0.05 were considered significant. All analyses have been performed using SAS software, version 9.2 of the SAS System for Windows.

4. Results

4.1. Clinical pathway implementation

As described in the materials and methods section, the clinical pathway was developed by the authors SB and AS following evidence based key interventions. The pathway was implemented on the Traumatology Department from January 2010 on. The following people were involved in the application of the clinical pathway:

- All surgeons, assistants and trainees involved in fragility hip fracture treatment: they include the patients in the clinical pathway as soon as they are hospitalized on the ward, either pre - or postoperatively, following the well-defined in- and exclusion criteria. Furthermore, they prescribe calcium and vitamin D to all included patients and inform the patients, their family and general practitioner about underlying osteoporosis, risk for subsequent fractures, importance of medical treatment and referral to the CMBD.
- Clinical pharmacist working on the ward: he or she performs follow-up and adjustment of the prescribed drugs when needed (calcium and vitamin D and other anti-osteoporosis treatment if preoperatively started) and checks renal function (minimum clearance of 35 ml/min needed for the safe administration of intravenous anti-osteoporosis treatment).
- Nurses on the ward: they administer calcium and vitamin D, and provide information to the patient and her / his family about the clinical pathway.
- Secretary on the ward: she makes the appointment for referral to the CMBD approximately six weeks postoperatively.
- Doctors and nurses working at the CMBD: they perform the following interventions:
    - For the patients above the age of 75: a comprehensive geriatric assessment, a DEXA-scan to establish a reference value of the bone quality, the administration of intravenous anti-osteoporosis therapy after control of the renal function and a fall risk assessment.
    - For the patients below the age of 75: a comprehensive geriatric assessment, a DEXA-scan, start of specific anti-osteoporosis medication if T-value < -2.5 and a fall risk assessment.

All co-workers involved in the implementation and execution of the clinical pathway were informed by SB and AS by means of information sessions and consultable

power point presentations. Two months after the introduction of the clinical pathway an evaluation meeting was organized by SB and AS with representatives of all co-workers involved. Some fine-tuning and practical adaptations were made to the pathway. Hereafter, the pathway was implemented in the Traumatology Department.

4.2. Evaluation

The following data were extracted from the patients' charts:

a. General characteristics of the included patients

A summary of patient characteristics can be found in Table 1. The intervention and the control group were comparable concerning age, gender, ASA-classification, fracture type, fracture treatment and follow-up time. The mean age of the patients was 81.2 (± 6.57) in the control group and 81.1 (± 6.87) in the intervention group. The male/female ratio was identical in both groups (± 1/3). The ASA-classification was comparable in both groups with most of the patients being ASA 2 or 3. The fracture classification was similar in both study groups with a nearly equal distribution of intra- and extracapsular fractures. The same equal distribution in treatment type could be noticed with slightly higher numbers of osteosynthesis than prostheses in both study groups. The mean follow-up time was 10 months in both study groups with a follow-up of one year in about 78% of the patients in both study groups as well. Only the number of preceding fractures was significantly higher in the intervention group than in the control group (52 compared to 24, $p<0.001$).

CHARACTERISTIC	CONTROL GROUP (N = 253)	INTERVENTION GROUP (N = 193)	P-VALUE
Age, mean ± standard deviation	81.2 ± 6.57	81.1 ± 6.87	0.914
Gender, n (%)			0.914
Female	187 (73.91%)	141 (73.06%)	
Male	66 (26.09%)	52 (26.94%)	
ASA-score, n (%)			0.653
1	13 (5.14%)	9 (4.66%)	
2	137 (54.15%)	94 (48.70%)	
3	97 (38.34%)	85 (44.04%)	
4	6 (2.37%)	5 (2.59%)	
Fracture type, n (%)			0.849
Intracapsular	130 (51.38%)	101 (52.33%)	
Extracapsular	123 (48.62%)	92 (47.67%)	
Treatment type, n (%)			0.499
Osteosynthesis	149 (58.89%)	107 (55.44%)	
Prosthesis	104 (41.11%)	86 (44.56%)	
Preceding fracture, n (%)			< 0.001
Yes	24 (9.49%)	52 (26.24%)	
No	229 (90.51%)	141 (73.06%)	
Follow-up			
Time (months), mean ± standard deviation	10.0 ± 3.86	10.1 ± 3.74	0.810
One year, n (%)	196 (77.47%)	151 (78.24%)	0.909

Table 1: Patient characteristics

b. Process parameters

An overview of the process parameters can be found in Table 2.

All process parameters were significantly better (all $p < 0.001$) in the intervention group than in the control group. More patients received anti-osteoporotic medication at discharge in the intervention group. Ninety-five % of patients in the intervention group received calcium and vitamin D compared to 38% in the control group. Furthermore, 61% of the patients in the intervention group received an anti-osteoporosis treatment in addition to calcium and vitamin D compared to 17% in the control group. A detailed analysis of patients' charts showed that this were mainly bisphosphonates. Usually, calcium, vitamin D and anti-osteoporosis medication were started postoperatively.

Significantly more patients from the intervention group were referred to the CMBD compared to the control group, Significantly more of the referred patients in the control group (100% or all of the referred patients) than in the intervention group (71%, $p < 0.001$) presented themselves at the CMBD. The time interval between hospitalization and referral to the CMBD was comparable in both study groups ($p = 0.090$). There was no difference in numbers of DEXA-scans performed between the control and the intervention group ($p = 0.809$). Finally, significantly more general practitioners of patients in the intervention group than in the control group were informed about postoperative care and follow-up details, with 90% ($p < 0.001$) of the general practitioners of the intervention group being informed.

PROCESS PARAMETER	CONTROL GROUP (N = 253)	INTERVENTION GROUP (N = 193)	P-VALUE
Osteoporosis treatment, n (%)			<0.001
No	155 (61.26%)	9 (4.66%)	
Yes	98 (38.74%)	184 (95.34%)	
- Calcium + Vitamin D, n (%)			<0.001
No	156 (61.66%)	10 (5.18%)	
Preoperatively started	51 (20.16%)	30 (15.54%)	
Postoperatively started	46 (18.18%)	153 (79.27%)	
- Other*, n (%)			<0.001
No	210 (83.00%)	75 (38.86%)	
Preoperatively started	24 (9.49%)	17 (8.81%)	
Postoperatively started	19 (7.51%)	101 (52.33%)	
Referral to CMBD, n (%)			<0.001
No	224 (88.54%)	14 (7.25%)	
Yes	29 (11.46%)	179 (92.75%)	
Compliance with referral, n (%)			<0.001
Non compliance	0 (0.00%)	52 (29.05%)	
Compliance	29 (100.00%)	127 (70.95%)	
DEXA			0.809
No	201 (80.08%)	156 (81.25%)	
Yes	50 (19.92%)	36 (18.75%)	
Information to GP, n (%)			<0.001
No	247 (97.63%)	20 (10.36%)	
Yes	6 (2.37%)	173 (89.64%)	

Table 2: Process parameters

(*mainly antiresorptive therapy)

c. Outcome parameters

An overview of the complications and reinterventions is provided in table 3. There were significantly more general complications in the intervention group compared to the control group (47.15% compared to 34.39%, p = 0.008). There were no differences in the number of local complications between the intervention and the control group (13.99% compared to 10.67%, p = 0.307). There were significantly more reinterventions in the intervention group compared to the control group (8.81% compared to 3.95%, p = 0.044).

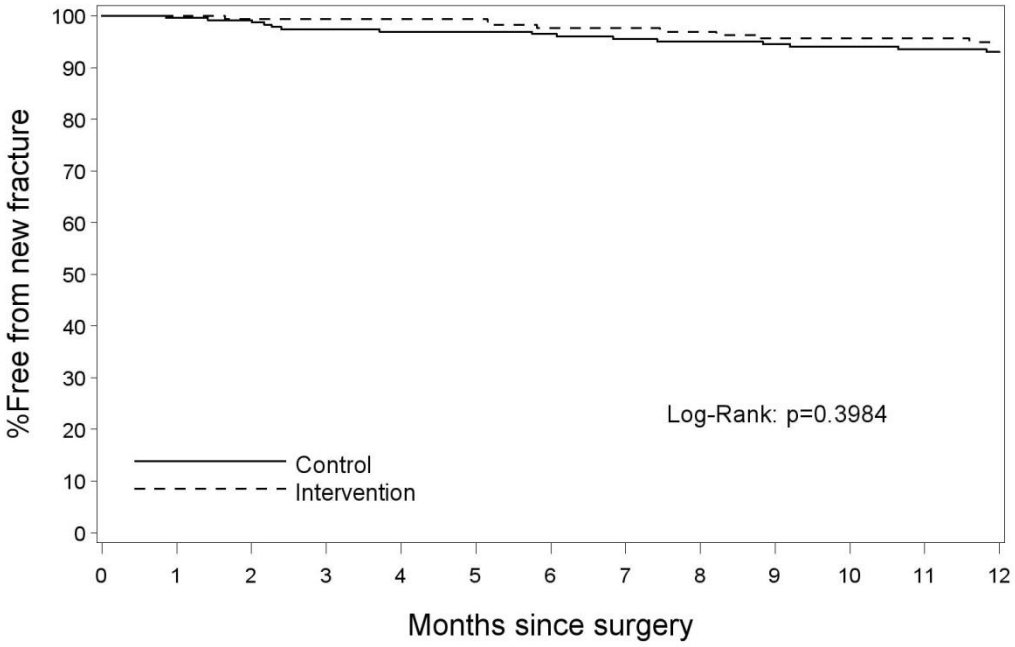
The time free from new fracture is displayed as a Kaplan-Meier estimate in Figure 1. In the year following the fracture, there were less patients with a recurrent fracture in the intervention than in the control group, however this difference was not significant (p = 0.3984). After eliminating the patients with a preceding fracture, there was no difference in time free from new fracture between the intervention and the control group (p = 0.7158) (Figure 2). Finally, overall survival during the first year following the fracture is displayed as a Kaplan-Meier estimate in Figure 3. Mortality rates for both groups are comparable at any time. At one year slightly more patients of the intervention group (93.07%, 95% CI = 88.33-95.93) were alive compared to the control group (91.51%, 95% CI = 87.24-94.40), however this difference is not significant (p = 0.4474).

	CONTROL GROUP (N = 253)	**INTERVENTION GROUP (N = 193)**	**P-VALUE**
General complications*, n (%)			0.008
Yes	87 (34.39%)	91 (47.15%)	
No	166 (65.61%)	102 (52.85%)	
Local complications**, n (%)			0.307
Yes	27 (10.67%)	27 (13.99%)	
No	226 (89.33%)	166 (86.01%)	
Reinterventions, n (%)			0.044
Yes	10 (3.95%)	17 (8.81%)	
No	243 (96.05%)	176 (91.19%)	

Table 3: Complications and reinterventions

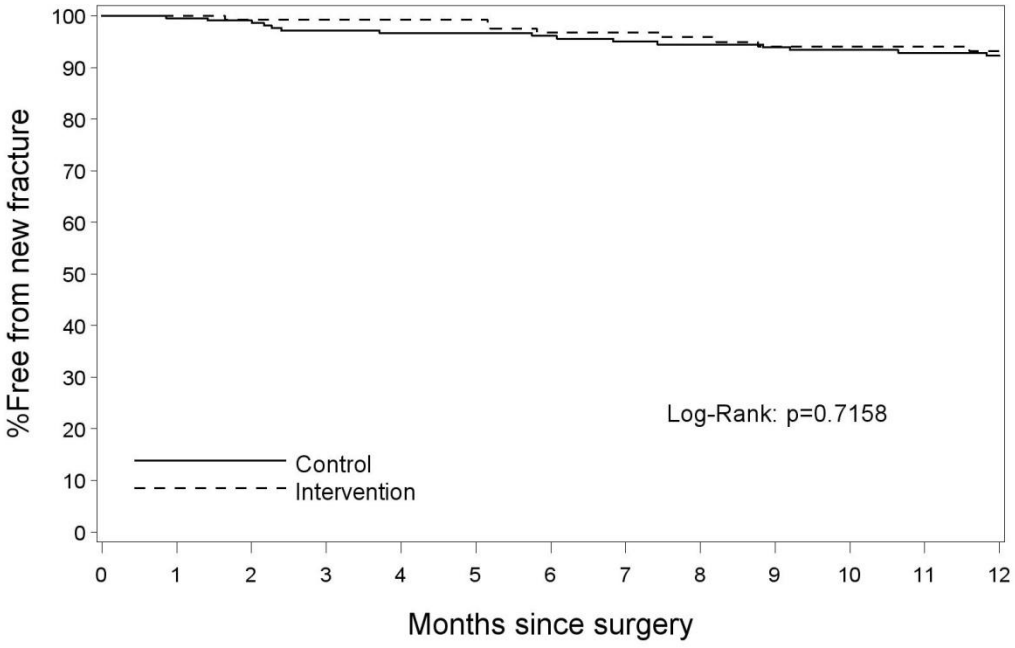
(* most frequently: cardiac failure, respiratory failure, urinary tract infection)

(**most frequently: wound infection, haematoma, periprosthetic fracture)



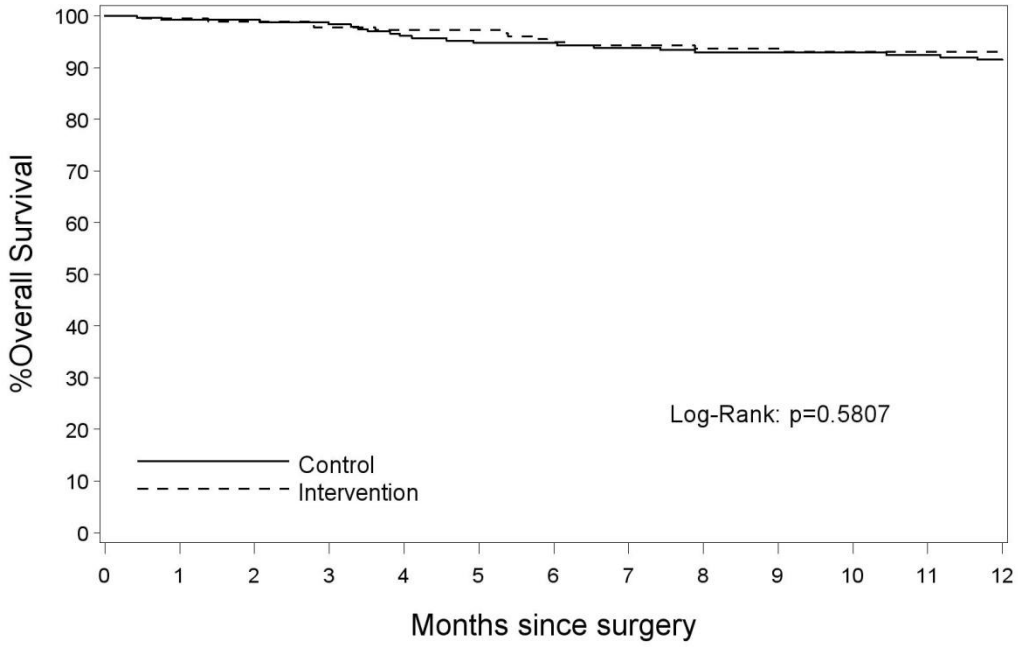
Number at risk													
Control	253	252	231	221	210	204	202	195	194	192	190	187	185
Intervention	192	192	177	169	166	163	158	152	149	146	145	145	144

Figure 1: Time free from new fracture (all patients)



Number at risk													
Control	229	228	209	199	190	184	182	175	174	172	171	168	166
Intervention	140	140	130	124	122	120	116	110	109	106	105	105	104

Figure 2: Time free from new fracture (only patients without preceding fracture)



Number at risk													
Control	253	251	233	225	216	210	209	204	202	201	200	197	195
Intervention	193	192	180	172	169	168	163	157	154	153	152	152	152

Figure 3: Overall survival

5. Discussion

5.1. Development, characteristics and added value of the clinical pathway

It was the aim of the actual study to develop a clinical pathway for secondary fracture prevention of fragility hip fracture patients. To call the intervention a clinical pathway, the following three requirements need to be fulfilled. At first, the intervention should be based on multidisciplinarity. Secondly, the content needs to be evidence based. Finally, the intervention should have an active follow-up.[11] The actual intervention is based on multidisciplinarity by its development and implementation by the collaboration of the Department of Traumatology and the CMBD with the presence of a geriatrician, endocrinologist and rheumatologist. Furthermore, paramedical co-workers of different services are involved in the implementation of the program (pharmacists, nurses, secretaries,...).

The content of the program is evidence based: randomized controlled trials advocate the administration of anti-resorptive therapy for the prevention of secondary fragility fractures with the concomitant administration of calcium and vitamin D.[14,21-23] The Belgian guidelines and reimbursement protocols are based on this evidence.[16] Finally, by the execution of the actual comparative study, the active recording and follow-up of the compliance to the program is clear and implicates the presence of the third requirement to call our intervention a clinical pathway.

In addition to the multidisciplinarity, our clinical pathway tries to be surgeon driven as more recent studies indicate the possible positive role of the surgeon on secondary fracture prevention.[24,25]

Finally, as it is clear that the economic consequences of fragility hip fracture treatment will only increase, the model of Miura[26] ("Hip Fracture Service": an interdisciplinary program to improve the care for frail elderly people with acute hip fracture using existing hospital resources) was used and our pathway was initiated by the use of the existing personnel and facilities, leading to a minimum of extra costs.

The decision to limit inclusion to patients, who are able to come to the CMBD on an ambulatory base, was based on the potential drawbacks of the pathway. So it was decided by the surgeon to consider the advantages of medical osteoporosis prevention, fall risk assessment and fall prevention measurements against the possible drawbacks, namely the effort to bring a bed-ridden and often not

communicating patient to the hospital. Mostly, this decision was taken after consultation of the family and the general practitioner.

5.2. Comparability of study groups

The intervention and the control group are comparable concerning mean age, gender differentiation, ASA-classification, fracture type, fracture treatment and time of follow-up. There only is a significant difference between the study groups concerning preceding fragility fractures: there are significantly more preceding fractures in the intervention group (table 1). As a prior fracture results in a 2-fold increased risk for a subsequent fracture,[1,10,27,28] we do not have an explanation for this difference. Despite the fact that all other characteristics of the study groups are comparable, the retrospective study design with the use of a historical control group could be prone to bias. Underreporting of previous fractures in the medical charts of the historical control group could also lead to this difference.

5.3. Process parameters

All of the three process parameters measured are significantly different between the study groups in favour of the intervention group (Table 2). Some authors strongly advise to optimize the treatment of the underlying osteoporosis at the moment of a fragility hip fracture by multidimensional interventions. In this context, we were able to make a difference by influencing three important process parameters with the implementation of our clinical pathway.

First, 90% of the patients of the intervention group were treated with calcium and vitamin D after the surgical treatment of their fragility hip fracture. This was evaluated by the presence of calcium and vitamin D in the medication list during hospitalization and on discharge. As described in literature, this information doesn't tell anything about compliance and long-term compliance is often poor.[19] The intake of calcium and vitamin D is a prerequisite for receiving antiresorptive therapy and in consequence (non)-compliance influences the effectiveness to prevent secondary fractures.

Secondly, the referral to the CMBD is significantly higher in the intervention group compared to the control group with nearly 93% of the patients receiving an appointment at discharge of the hospitalization for their hip fracture. Nevertheless, only 70.55% of these patients do show up at the CMBD compared to 100% of the

patients of the control group ($p < 0.001$). This low number can be explained by the *systematic* referral of the patients of the intervention group. The patients of the control group are only referred to the CMBD on their personal request, so their intrinsic motivation and compliance as well might be higher. Informing the patients and their representatives about osteoporosis management by an osteoporosis case manager could even improve information transfer and compliance with follow-up procedures. [29]

Furthermore, equal numbers of patients from the control and intervention group undergo DEXA-scanning when coming to the CMBD (19.92% of the patients in the control group compared to 18.75% of the patients in the intervention group, $p = 0.809$). This low number of DEXA-scans can be explained by the fact that a fragility hip fracture in itself is defined as a symptom of osteoporosis and leads to reimbursement of antiresorptive therapy in the Belgian health care system.[7,16] DEXA-scanning is only performed to define reference values for the follow-up of long-term treatment.

Finally, we were not able to include information about fall risk assessment and fall preventive measurements in our study as the registration of these data was not performed in a standardized way. As the prevention of falls is part of the postoperative osteoporosis management as well[7,17], this is an important point for improvement.

5.4. Outcome parameters

The intervention group suffered from a significantly higher number of general complications compared to the control group. This is probably due to a better reporting in the intervention group as a non-intended consequence of the implementation of our clinical pathway. There were also significantly more reinterventions in the intervention group although the number of local complications was only slightly and not significantly higher than in the control group (Table 3). This can possible be explained by a general change in the care for fragility hip fracture patients. Together with the implementation of the care pathway, more attention was given to local postoperative complications. The threshold to drain a postoperative haematoma or debride a wound because of suspected infection, was much lower than in the years before.

Our clinical pathway did not have a protective effect on the occurrence of recurrent fractures (Figure 1), even not in the subgroup of patients without a preceding fracture (Figure 2). The pathway had no effect on the 1-year mortality (Figure 3). At first sight, it could be disappointing that we were not able to show a strong effect with our intervention. Based on the Kaplan-Meier curve, we observed a 1-year refracture rate of 7% in the control group. Given this relatively low event rate, large samples sizes are needed to detect clinical relevant improvements. For example, with the current number of included subjects (N=446) there was 60.6% power to detect a halving of the refracture rate in the intervention group (i. e. 3.5%). This is based on a two-sided log-rank test with alpha=5%, assuming all patients having a follow-up of 12 months, an equal number of patients in both groups and an exponential distribution of the event times. The actual power of the study even turns out to be a bit lower, since not all patients have complete follow-up and since there is an imbalance in the number of patients (57% in control group, 43% in the intervention group). Even to detect a stronger effect of the intervention (2% versus 7% refracture rate) the study is slightly underpowered, i.e. the power equals 72%.

Furthermore, it is striking that the mortality rate in general for the study and the control group is much lower than the expected mortality rate for fragility hip fracture patients with numbers reported as high as 20 to 30%.[6,7,12,30] This finding might be explained by the fact that there is a strong patient selection by the exclusion of non-ambulatory patients. In this way, probably the patients with the most comorbidities, functional impairment, frailty, and limited life expectancy were excluded. This selection bias however was implemented on an arbitrary base as explained before. Finally it has been shown extensively that it is very difficult to include long-term mortality in studies on geriatric hip fracture treatment. In our own systematic review of the literature and meta-analysis (Chapter I) we could only show a significant difference in long-term mortality for the non-randomized studies. As stated by other authors as well, this might be due to the heterogeneity of the included studies with a big variation in the content or the interventions of the studied clinical pathway.[31] Furthermore, mortality might not be the best outcome parameter to evaluate in this patient population as it might be influenced by a lot of other causes as well.[8] A study on which set of outcome parameters to be used for this frail patient population also included parameters evaluating functionality (mobility, activities of daily living) besides other parameters like complications and re-admissions.[32]

5.5. Limitations of the study and outlook

The limitations of the actual study can be summarized as follows.

First, it is a retrospective study with a historical control group conducted by review of the patients' charts. This might explain that there are a lot of missing data: we don't have information of patients being treated for a complication or recurrent fracture in another hospital nor of patients with an uneventful postoperative evolution who were lost for follow-up.

Secondly, the intended follow-up time in our study was one year with a realized mean follow-up time of 10 months in both the control and intervention group (Table 1). Moreover, the time to referral to the CMBD was 77 days in the intervention group and 95 days in the control group. Together with a mean follow-up time of 10 months, the follow-up time after the administration of antiresorptive therapy was only 7 months. In the large-scale studies on antiresorptive therapy[14,33], the relative risk reduction of recurrent hip fractures started at 12 months and progressively increased until the end of follow-up at 36 months. So prospective large-scale (multicenter) studies with a longer follow-up time will be definitely needed to solve this issue. In the actual context of limited health resources, the findings of these kinds of studies will be of utmost importance to balance the costs of pharmacological osteoporosis treatment against the efforts needed to increase patient compliance. In the meantime, it should be good to consider non-pharmacological refracture preventive measurements as well. Literature shows evidence for dietary measures (calcium and vitamin D suppletion) but the effectiveness of fall prevention strategies on the incidence of recurrent fractures is less clear[7,34,35], so in this area as well further research is needed. For our study more specifically, efforts need to be made to integrate a fall evaluation program and measures for fall prevention in the program and to document these data in the patients' charts. Finally, the information transfer on the prevention of recurrent osteoporotic fractures to the patient, his relatives and their general practitioner should be adjusted. An introduction of an osteoporotic case manager in the traumatology department and providing patient information leaflets on hospital entry with a hip fracture, are the next steps to adjust our traumatologic-geriatric postoperative program for hip fracture patients.

6. Conclusion

In this retrospective study, a traumatologic-geriatric post-fracture program for the prevention of osteoporotic recurrent fractures in geriatric hip fracture patients was not associated with a significant reduction in the number of recurrent fractures nor with a mortality reduction within the first year after the fracture. Nevertheless, a significant difference was observed between the two study groups for all process indicators. Options for further improvements of this program to optimize postoperative care for hip fracture patients need to be investigated. There is no doubt that the actual clinical pathway induced an awareness in co-workers for the problem of osteoporotic recurrent fractures and for interdisciplinary management of these complex patients.

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Chapter III

Biomechanical evaluation of bone-cement augmented proximal femoral nail antirotation blades in a polyurethane foam model with low density

This chapter has been published as:
Sermon A, Boner V, Schwieger K, Boger A, Boonen S, Broos P, et al. Biomechanical evaluation of bone-cement augmented Proximal Femoral Nail Antirotation blades in a polyurethane foam model with low density. Clin Biomech 2012; 27: 71-76

1. Abstract

Background: Helically shaped cephalic implants have proven their benefit to provide an improved stabilization of unstable hip fractures. However, cut-out ratios up to 3.6% still occur. This in vitro study evaluated the biomechanical performance of a novel cement augmentation technique of the Proximal Femoral Nail Antirotation in surrogate femora.

Methods: Four study groups were formed out of 24 polyurethane foam specimens with low density. Proximal Femoral Nail Antirotation blades were implanted, either non-augmented, or augmented using 3 milliliters of injectable Polymethylmethacrylate bone-cement. The influence of implant malpositioning was investigated by placing the blade either centered in the femoral head or off-centric in an anteroposterior direction. All specimens underwent cyclic loading under physiological conditions. Starting at 1000 Newton, the load was monotonically increased by 0.1 Newton/cycle until construct failure. Movement of the head was identified by means of optical motion tracking. Non-parametric test statistics were carried out on the cycles to failure, to compare between study groups.

Findings: Compared to control samples; augmented samples showed a significantly increased number of cycles to failure ($P = 0.012$). In the groups with centric position of the Proximal Femoral Nail Antirotation blade, cement augmentation led to an increase in loading cycles of 225%. In the groups with off-centric positioning of the blade, this difference was even more accentuated (933%).

Interpretation: Cement augmentation of the Proximal Femoral Nail Antirotation blade with small amounts of bone-cement for treatment of osteoporotic hip fractures clearly enhances fixation stability and carries high potential for clinical application.

2. Introduction

Among fragility fractures, hip fractures constitute the most dramatic complication of osteoporosis and a major public health concern. From a clinical perspective, the major concern is the associated morbidity and mortality. Up to 25% of fragility-related hip fracture patients die in the year following their fracture and of those who do survive, again some 20% will have to be institutionalised because of the fracture and its clinical consequences.[1-5] Because of the aging of the population, the incidence and costs related to hip fractures will continue to increase exponentially. By 2025, there will be an estimated more than three million of annual incident fractures in the United States, creating direct medical costs of $ 25 billion.[6] Despite new developments in the management of age-related osteoporosis, a lack of awareness continues to contribute to underdiagnosis and undertreatment of the disease.[7] In addition to surgeon-dependent factors like quality of reduction and correct positioning of the implant, bone quality plays a major role in the occurrence of fixation failure.[8-10] Especially cut-out, a failure mechanism characterized by migration of the implant through the cancellous bone of the femoral head, is significantly related to the bone mineral density of the proximal femur.[11,12] Cut-out ratios up to 12.6% are reported in literature when using screw-based fixation types like the *Dynamic Hip Screw (DHS)*, *Gammanail* or *Proximal Femoral Nail (PFN)* for the treatment of unstable intertrochanteric fractures.[13-18] Helical and spiral blade concepts have been proven to biomechanically improve resistance to cut-out.[19,20] However, cut-out ratios of the *Proximal Femoral Nail Antirotation (PFNA)* of up to 3.6% are still seen in clinics.[18,21,22] The application of bone-cement based on for example, polymethylmethacrylate (PMMA) could potentially further reduce the risk of cut-out in severe osteoporotic cases. Biomechanically, a clear benefit of cement augmentation has already been demonstrated as exemplified by dynamic hip screw instrumentations placing the implant into an afore-injected cement volume.[23,24] Improved resistance to cut-out is believed to relate mainly to an increase in implant surface with reduced stress on the trabecular structure. Clinically, the first attempts of implant augmentation with promising outcome were reported back in 1985.[25] Surprisingly however, the technique never became clinical routine. This is most probably because of the concerns in the medical community regarding interference with fracture healing due to excessive cement application and the presence of

cement at the fracture site, the possible damage to periosteal blood supply leading to femoral head necrosis, leakage of PMMA into the hip joint and the difficulties regarding implant removal.[24-28] Some of these objections however have already been disproven: nonunion can be avoided by keeping the cement to the proximal fragment and out of the fracture site.[25] Furthermore newly designed implants which allow for augmentation through the implant, will prevent cement leakage into the hip joint or into the fracture area.[24,26] Finally, thermal necrosis can be avoided by the use of limited amounts of PMMA (not more than 3ml).[29] By changing the properties of the PMMA and making it more viscous, the risk of cement leakage can even be further minimized.[30]

In the current study, perforated PFNA-blades were augmented with 3 ml of an injectable medium to high viscosity PMMA cement. The cannulation of the implant and additional perforations allow for injection of the cement into the surrounding bone tissue subsequent to implant insertion. Hence, a decision in favour or against cement augmentation can be taken intra-operatively after the implant has been placed. The aim of our study was to biomechanically compare cut-out resistance and rotational stability under cyclic loading of PMMA augmented PFNA-blades with non-augmented instrumentation in surrogate femoral heads. In order to be able to provoke failures, a suboptimal implant positioning was chosen and this in two ways. First of all, in the study groups with center-center blade position, a tip-apex distance of 24 mm was chosen as the blade was inserted to a depth of 38 mm. In the study groups with an off-centric blade positioning of 7 mm to the antero-posterior direction, this resulted in a tip-apex distance of 25.89 mm. According to the literature, this rather large tip-apex distances would make the specimen more prone to cut-out.[9] Secondly, an off center position of the helical blade would create a moment arm, making the construct rotationally unstable.

3. Materials and methods

3.1. Specimens and instrumentation

A total of 24 surrogate specimens with defined geometry were manufactured of cellular polyurethane foam (10pcf, 1522-10, Pacific Research Inc., Malmö, Sweden). This closed cell foam represents a standardized and uniform material with properties in the range of human cancellous bone. A density of 10 pcf (pounds per cubic foot, 160.2 kg/m³) was chosen to mimic an osteopenic bone structure.[31] Four study-groups (augmented / non-augmented with centered or off-centered implant position) were formed, each comprising of 6 samples (Table. 1).

Group	Treatment	Implant position
1	Non-augmented	Center
2	Augmented	Center
3	Non-augmented	Off-center
4	Augmented	Off-center

Table 1: Study design in terms of study groups

The foam specimens (length 50 mm, width 38 mm, height 50 mm, Fig. 1a) were confined to a custom-made polymer shell (diameter 56 mm) mimicking the cortex of the femoral head for subsequent load introduction. With the aid of a special jig, a 3.5-mm guide-wire was inserted into the foam either centered (groups 1 and 2) or with a 7 mm antero-posterior offset (groups 3 and 4) generating a moment towards negative pitch of the blade under physiological loading conditions (Fig.1b). Standard PFNA-blades (length 100 mm, Synthes GmbH, Bettlach, Switzerland) were inserted over the guide-wire without predrilling to a depth of 38 mm, yielding a 12 mm distance between the implant tip and the apex of the foam (Fig. 1c). For the augmented groups 2 and 4 modified PFNA-blades (length 100 mm, Synthes GmbH, Bettlach, Switzerland) with 12 lateral perforations were used (Fig. 2). To inject the bone-cement, the guide-wire was removed and a side opening cannula (Vertebroplasty Needle Kit, 8 Ga, Article number: 03.702.216S, Synthes GmbH, Oberdorf, Switzerland, Fig. 2) was inserted into the cannulation of the implant to the full depth. The side opening at the tip of the cannula was enlarged to a dimension of 3 x 12 mm.

Injection of 3 ml PMMA bone-cement (Vertecem V+, Synthes GmbH, Oberdorf, Switzerland) was done in a standardized manner: after mixing of the components, the cement was filled into 3.0 and 1.0 ml syringes (Viscosafe Injection Kit, Article number: 07.702.210, Synthes GmbH, Oberdorf, Switzerland).[32] First of all, the cannula was prefilled with 3.0 ml of PMMA. Subsequently, 1.0 ml of PMMA was injected through the perforations of the blade into the foam towards cranial. After turning the cannula by 180°, another 1.0 ml was injected. Finally, the cannula was withdrawn by 10 mm and the procedure was repeated injecting 0.5 ml cement towards cranial and 0.5 ml towards caudal.

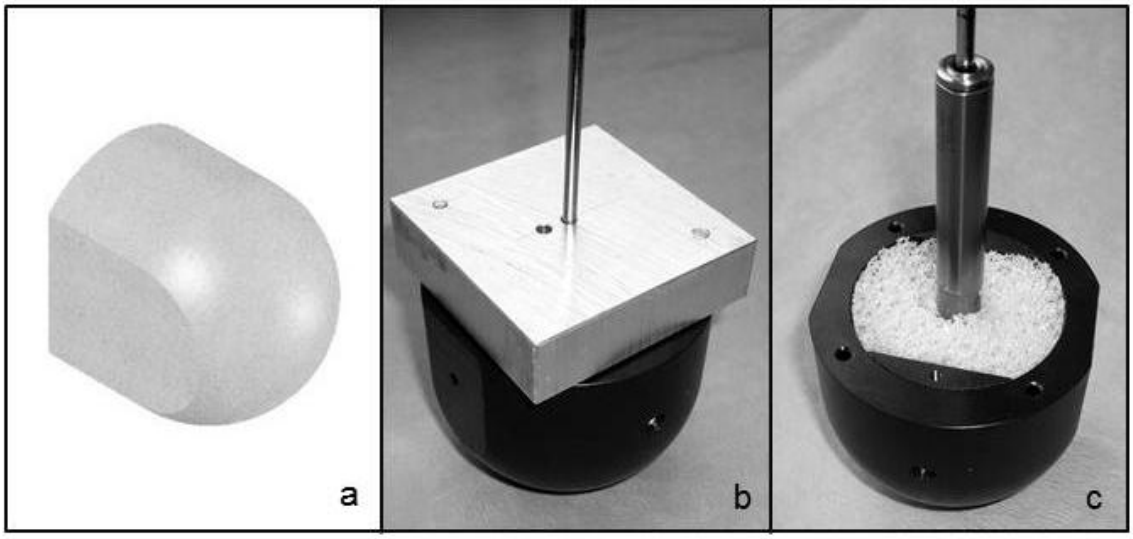

Figure 1: Foam specimen and instrumentation

1a: Foam specimen.

1b: Foam specimen confined to polymer shell with custom-made jig on top for guide-wire placement either in the centre of the femoral head or at 7 mm anteroposterior offset.

1c: Insertion of the PFNA-blade to a standardised depth.

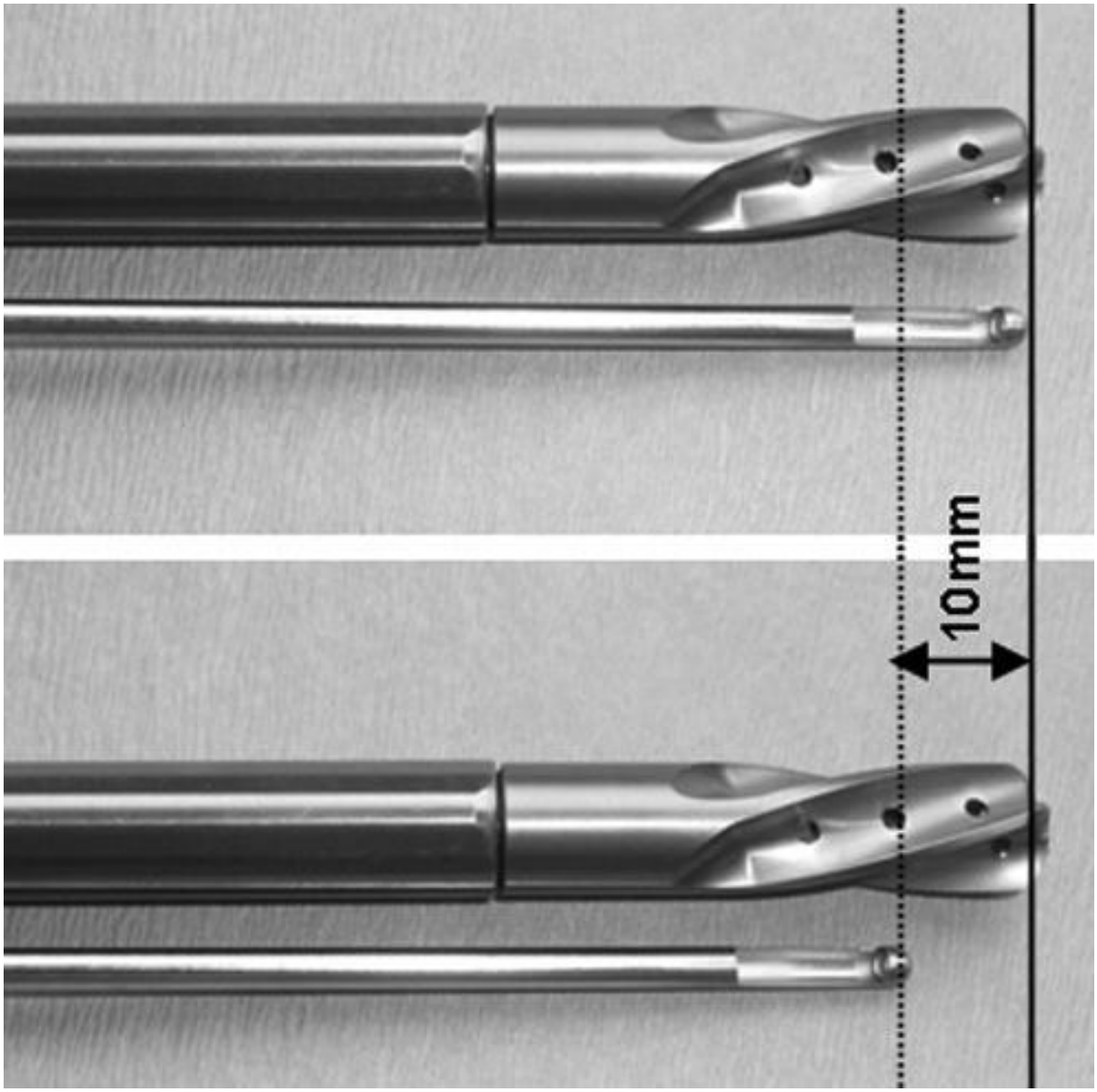

Figure 2: Modified PFNA-blade with 12 lateral perforations for cement injection. A side-opening cannula was used for controlled cement application. The cannula was first inserted into the implant cannulation to the full depth to inject 2 ml of bone cement and then withdrawn by 10 mm to inject another 1 ml.

3.2. Mechanical testing

Mechanical testing was conducted according to the model described by Sommers et al. simulating an unstable intertrochanteric fracture with lack of postero-medial support and load sharing at the fracture gap.[33] Implant shafts were rigidly mounted to a base fixture at 149º to the horizontal plane. This setting reflected a 130º femoral neck angle, a 16º resultant joint load vector to the vertical plus 3º offset of the femoral shaft axis from the sagittal plane (Fig. 3a and 3b). The femoral surrogates were confined in a plastic shell to simulate the characteristics of a reduced unstable intertrochanteric fracture. A polymer back plate rested on two cylindrical rollers allowing the head to collapse into varus. The implant was free to slide mimicking full implant dynamic. Testing was performed on an MTS Mini Bionix II 858 hydraulic test system (MTS Systems Corp., Eden Prairie, USA) equipped with a 4 kN load cell. In order to simulate an alternating load during walking, a loading trajectory measured in vivo in the human hip was transferred to the femoral head. The curve was provided by Bergmann et al.[34] Starting at 1000 N the load was monotonically increased by 0.1 N/cycle until failure of the construct according to the protocol of Windolf et al.[19] The load-valley was maintained at 100 N throughout the test. Cyclic testing was performed at 2 Hz. Testing was stopped when the crosshead displacement exceeded 7 mm.

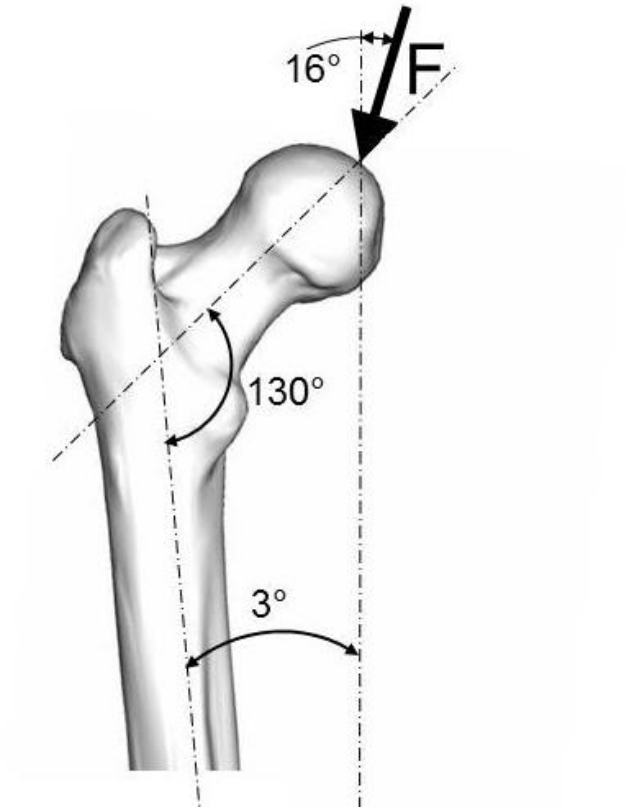

Figure 3a: Illustration of the simulated force introduction at the proximal femur according to Sommers et al, 2004: an assumed tilting of the femoral shaft of 3°, a 130° CCD angle of the implant plus a 16° offset of the resultant hip joint contact force to the vertical results in a 149° angle between implant axis and direction of the force.

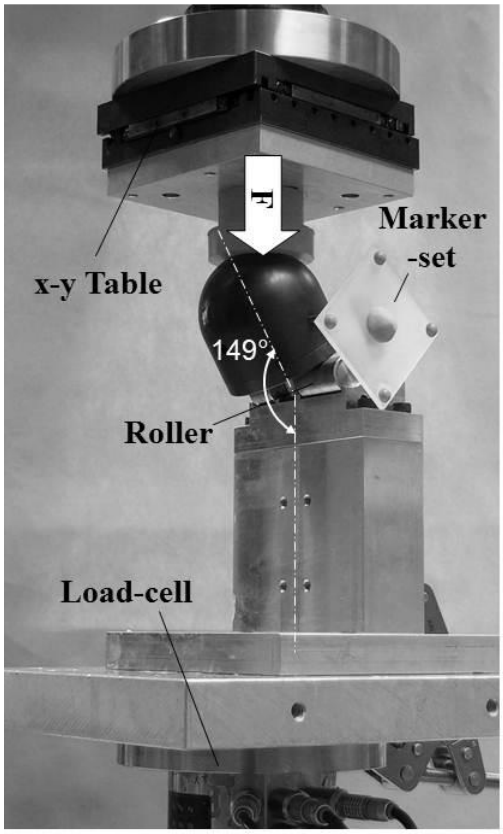

Figure 3b: Test set-up: the sample is free to rotate about the implant axis and could collapse into varus. An x-y table compensates the resulting displacements. A set of retro-reflective markers allows for detection of the head motion in six degrees of freedom. A second set of markers was attached to the shaft of the implant (not visible here) to measure migration of the implant. A physiological loading trajectory is transferred to the head in physiological orientation and is cyclically increased until failure of the construct (arrow “F”). The 149° angle between the implant axis and the direction of the force is also shown.

3.3. Data acquisition and evaluation

Using an optical 3D motion tracking system with five ProReflex MCU digital cameras (Qualisys AB, Gothenburg, Sweden) the motion of the surrogate femoral head in terms of varus rotation and rotation around the implant axis was evaluated throughout the experiment. A reflective marker set was attached to the plastic shell (Fig. 3b). Additionally, a set of markers was attached to the shaft of the PFNA-blade in order to measure implant migration. For statistical analysis, failure criterions were set to 5° varus collapse and 10° rotation about the blade axis (Fig. 3c and 3d). Blade migration was defined as displacement of the implant tip greater than 1 mm. Number of cycles until failure at unloading condition (plastic deformation) was determined for each failure criterion. After checking the data for normal distribution (Shapiro-Wilk test), non-parametric test statistics were carried out. Multiple Mann-Whitney-U tests were performed on the cycles until failure for pairwise comparisons between study-groups. *P*-values were corrected according to Bonferroni. Significance level was set to $\alpha = 0.05$.

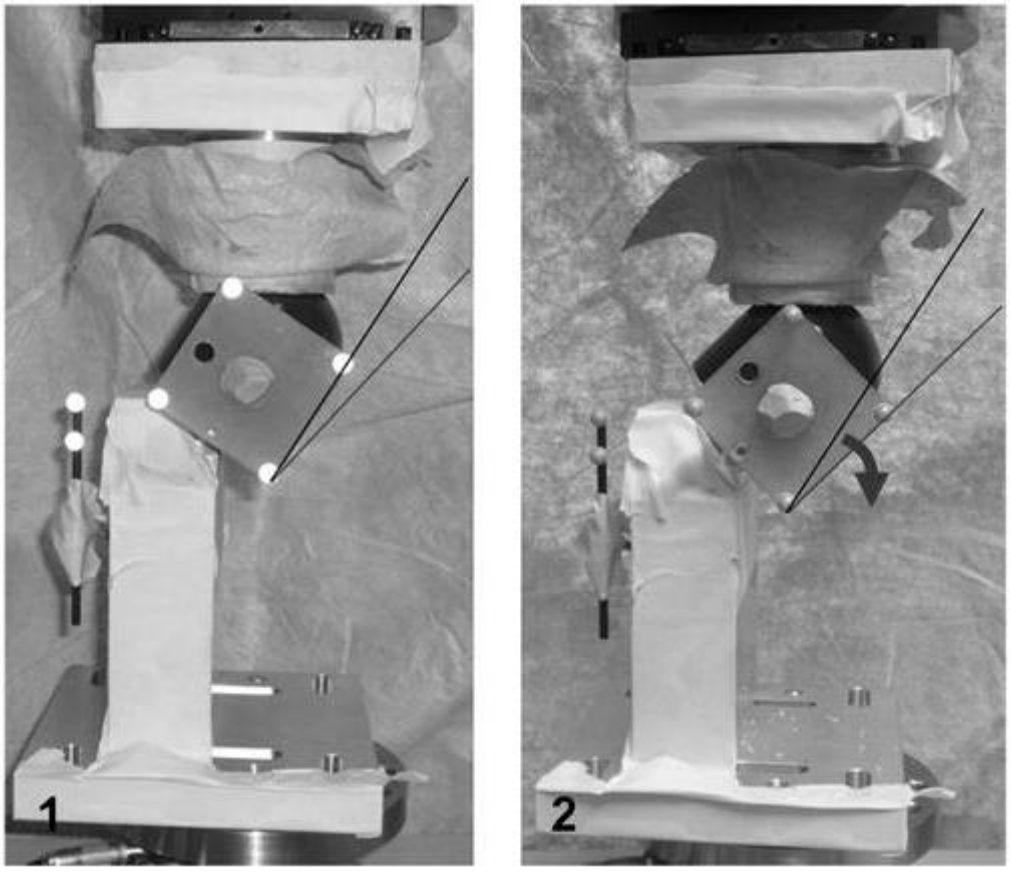

Figure 3c: Varus collapse, the movement is indicated by the arrow.

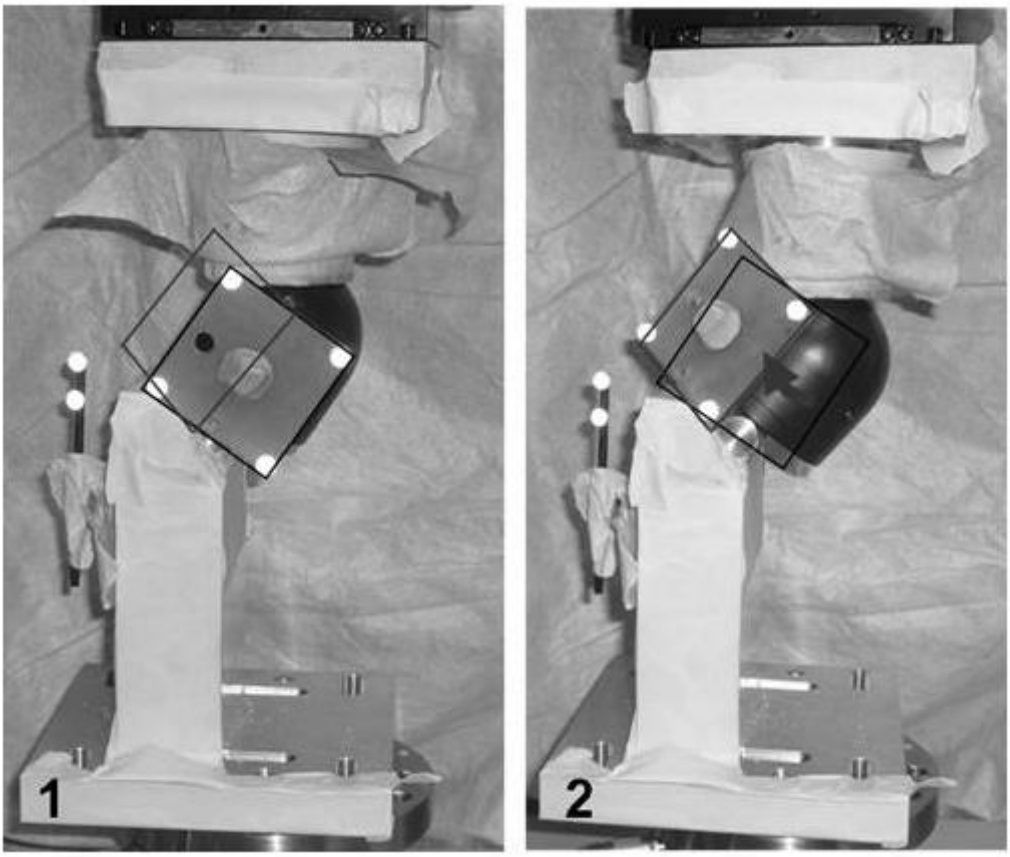

Figure 3d: Rotation around the blade axis, the movement is indicated by the arrow.

4. Results

Compared to control samples, augmented samples showed an increased number of cycles to failure. The samples of the non-augmented groups 1 and 3 failed by cut-out of the implant, resulting in a varus collapse of the femoral head. In the presence of augmentation, the cement was split into a cranial and a caudal segment (Fig. 4). No severe damage of the implants was observed during the tests. For centric position of the PFNA-blade, the number of cycles to 5° varus rotation of the head was mean 8,317 (SD 1,205) for the non-augmented group (1) compared to mean 27,025 (SD 3,077) for the augmented group (2). This reflects a 225% increase in load cycles due to augmentation. This difference was even more pronounced in the study-groups with eccentric implant position (933% increase). Cycles to 5° varus collapse of the head were mean 1,992 (SD 1,771) for the non-augmented specimens (group 3) compared to mean 20,575 (SD 1,548) cycles when augmentation was performed (group 4). All pairwise comparisons between study-groups regarding varus rotation revealed statistically significant differences (all $P = 0.012$). Figure 5 shows the varus rotation of all groups in the course of testing. In contrast to the specimens with centric blade position, all specimens of the groups with off-centric blade placement (groups 3 and 4) revealed additional head rotation around the blade axis. Number of cycles to 10° head rotation was mean 1,200 (SD 1,376) for the non-augmented off-center group (3) and mean 20,575 (SD 1,548) for the augmented off-centric specimens (group 4). This difference was significant between groups ($P = 0.002$) (Fig. 6). In the off-center group without augmentation (3), 3 out of 6 samples showed early failure due to backing out of the blade (migration > 1 mm). As soon as the test started, the blade tended to wander out of the surrogate towards distal with simultaneous rotation of the femoral head.

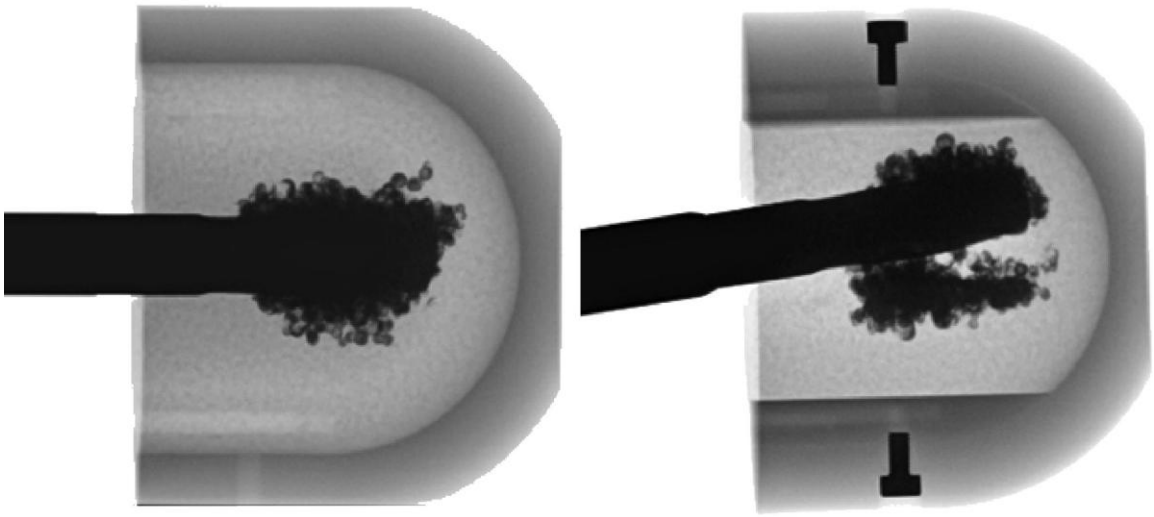

Figure 4: Radiographs of an instrumented specimen before (left) and after testing (right). Left: A cement cloud surrounding the PFNA-blade increases the anchorage. Right: After intensive loading, the cement volume is split and the specimen shows typical varus collapse as clinically seen in the presence of cut-out.

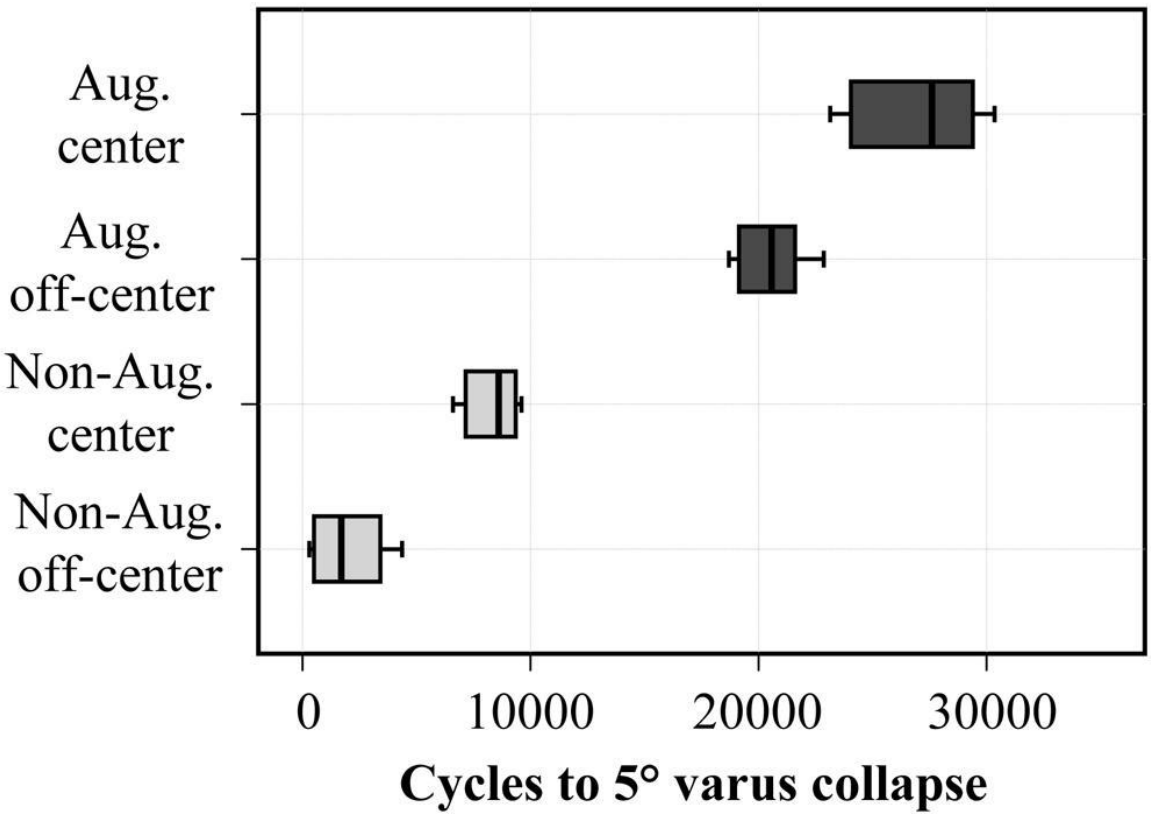

Figure 5: Boxplots of the number of cycles until 5° varus collapse of the femoral head for all study groups. The augmented samples with centric implant position revealed the highest stability; the non-augmented, eccentric specimens failed earliest in the course of testing. All groups were statistically different with respect to each other (all $P = 0.012$).

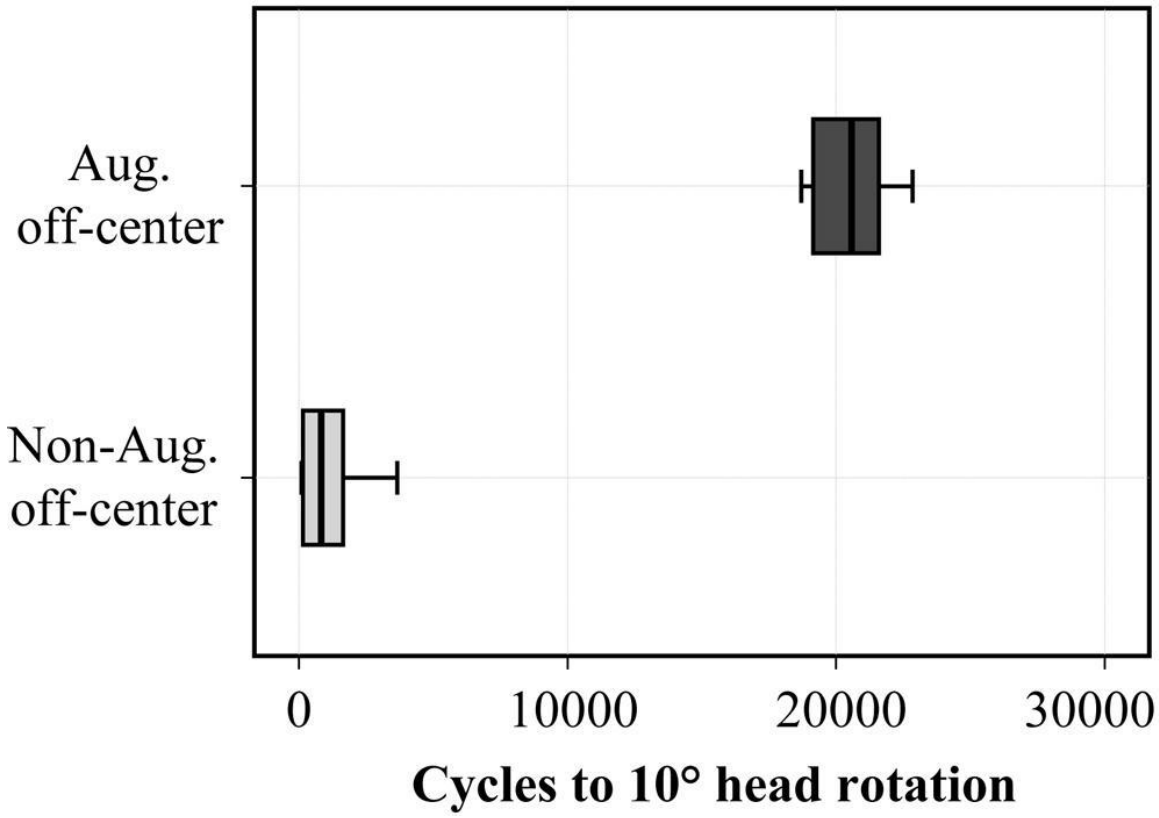

Figure 6: Boxplots of the number of cycles until 10° rotation of the sample about the implant axis for the study groups with eccentric implant position. The centrically placed specimens did not exceed this failure criterion. A highly increased stability due to augmentation is obvious.

5. Discussion

The problem of fixation failure of cephalic hip implants for the treatment of intertrochanteric fractures is well known. Causes can be divided into two major groups. First of all, there are a number of surgeon and surgical technique related issues, like insufficient reduction or suboptimal positioning of the implant.[25,35] Secondly, fixation failures are more likely to occur in osteoporotic bone.[8]

New implant designs have improved failure rates but cut-outs remain an issue.[21,22] Because osteoporosis continues to be underdiagnosed and undertreated, surgical options are mandatory.[12,36] Both in biomechanical and clinical studies, the technique of cement augmentation of cephalic implants to increase the anchorage in osteoporotic femoral heads has been successfully introduced.[24-27,37,38]

This in-vitro study evaluated a novel PMMA augmentation concept of the helical blade of the *Proximal Femoral Nail Antirotation* (PFNA) in terms of cut-out resistance and rotational stability using surrogate femoral heads. The augmented implants with centered position showed an increase in the number of cycles to fatigue failure by 225% when compared to non-augmented controls. In cases of eccentric implant placement, this difference was even more pronounced. In agreement with other studies, these results strongly suggest that augmentation enhances implant anchorage and carries potential to prevent fixation failure, even in cases with mal-positioned hardware.[24,25] However, in the first instance, augmentation is meant to compensate for reduced bone quality.

Our study showed that off-centered positioning affects implant purchase even when associated with augmentation. Misinterpretation of the method as “all-purpose tool” against cut-out should be avoided in any case. Proper fracture reduction and accurate implant positioning remain key factors to achieve a satisfying surgical outcome.

Before augmentation can be embedded into the existing surgical technique, some additional steps are needed. One strategy could be to use perforated implants. The same implant could then be used solely or combined with augmentation. The decision to augment can be taken during the surgical intervention on the basis of distinct criteria. The opportunity to inject bone-cement after placing the implant represents a clear advantage in terms of safety. Major complications, like missing the implant insertion during the curing period of the cement, can be excluded. No implant

failures were observed during the course of testing. A relatively viscous type of PMMA cement was used. It was technically feasible to inject the PMMA but a comparatively high injection pressure was required. 1 ml syringes provided a feasible transmission of the injection forces and allowed for controlled cement application. By using injectable medium-to-high viscosity PMMA, undesired cement leakage may be avoided.[32] Cement portions could block the sliding capability of the implant or could squeeze into the fracture site. This might lead to healing complications like non-unions, persistence of non-reducible fracture gaps and interference with periosteal healing.[26,39] To minimize the risk for avascular- and heat-necrosis during PMMA polymerization, and, in more general terms, to follow the principle of minimal alteration of an existing biology, a limited amount of PMMA (3 ml) was used.[28,29] Excessive application of PMMA could destruct cartilage because of subchondral cement localization, or could generate fat emboli. In addition, excessive amounts of PMMA alter the risk of infection[25] due to the potential space for bacteria adhesion and the possible tissue necrosis associated to heat generation. With respect to implant removal, no problems were encountered when withdrawing the blade from the cement volume. Removal of the blades was performed on each test specimen with the dedicated instrument and following the surgical technique as provided by the manufacturer. The extraction screwdriver was attached to the blade by turning it counter clockwise and gentle blows were applied with the hammer. As mentioned by other authors, the cement sheared completely off the implant.[40] The relicts of bone-cement could complicate revision surgeries but drillable PMMA, as used in this study, allows for anchoring implants in a hardened state. The use of alternative biomaterials like degradable Calcium-Phosphate cements might be an option for the future. However, the mechanics of current formulations, especially concerning shear[27], are still not comparable to PMMA based solutions in load bearing applications.

A polyurethane foam model with comparatively low density was used to imitate severely osteoporotic bone. The foam type was chosen from pilot experiments to achieve an acceptable compromise between loading regime, number of test-cycles until fatigue failure, and failure patterns. All parameters were in line with those in previous test trials using human cadaver bones in the same setting. However, the question to what extent our results can be extrapolated to clinical practice remains open.

The use of synthetic bone structures for biomechanical testing is still subject to ongoing debate et al.[41,42] The foam we used showed closed porosity, which might alter cement distribution compared to an open trabecular structure. However, the derived cement volumes surrounding the implants appeared homogenous and were comparable to the infiltration observed in cadaver samples. In human bones, trabecular structure and bone density might vary along the blade axis, which could lead to a more scattered cement distribution. However, as shown in another study, our cement was optimized to enhance uniform filling.[32]

Our test setup simulated the dynamic situation of a reduced, unstable intertrochanteric hip fracture after completion of implant sliding.[33] A controlled load sharing between implant and fracture site was established. Since our focus was on the implant-bone interface, an isolated head model was deemed as most practical despite though general limitations. To avoid secondary failures, PFNA-nail and femoral shaft fragment were not considered, limiting the modelling of the actual biomechanical situation to an acceptable extent. The center of varus-rotation was statically located at the center of the roller, whereas the actual rotational center might dynamically migrate. The polymer shell confining the head samples does only marginally compare to the anatomical dimension of a femoral head which alters the acting lever arm between joint force vector and implant. However, the observed failure patterns like a varus collapse of the femoral head were comparable to the ones seen in clinic, supporting clinical relevance of our model. Cyclic testing was performed using an in-vivo measured loading curve simulating the main forces acting in the hip joint during gait.[34] A 3D motion analysis system was used for data acquisition because spatial movement of the head fragment had to be assessed. Assuming test fixture and implant as rigid, a reference marker-set was not installed. Compliance of the system was therefore neglected.

To interpret our findings with more confidence, follow-up investigations on fresh frozen cadaveric femoral heads should include assessment of bone mineral density. Ultimately, the full operational procedure should be evaluated in a clinical setting. Potential issues associated with cement injectability, cement leakage, implant removal and revision surgeries will require further assessment before bringing this promising technique into clinical practice.

6. Conclusion

The technique of implant augmentation using bone-cement appears to significantly enhance the implant anchorage in a context of poor bone quality. Our promising in vitro results suggest that augmentation of the PFNA–blade with small amounts of PMMA cement in the treatment of osteoporotic hip fractures clearly enhances fixation stability and carries high potential for clinical application.

7. Conflict of interest statement

The authors are not compensated and there are no other institutional subsidies, corporate affiliations, or funding sources supporting this work unless clearly documented and disclosed: partial funding was received from Synthes GmbH who also kindly provided the implants and bone cement.

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Chapter IV

Potential of PMMA cement-augmented helical PFNA blades to improve implant stability – a biomechanical investigation in human cadaveric femoral heads

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This chapter has been published as:
Sermon A, Boner V, Boger A, Schwieger K, Boonen S, Broos P, et al. Potential of polymethylmethacrylate cement-augmented helical proximal femoral nail antirotation blades to improve implant stability - A biomechanical investigation in human cadaveric femoral heads. J Trauma 2012; 72: 54-59

1. Abstract

Background: Cement augmentation may improve fixation stability and reduce cut-out rate in the treatment of intertrochanteric hip fractures. The aim of this study was to compare the number of cycles to failure of polymethylmethacrylate-augmented helical blades with non-augmented ones in human cadaveric femoral heads.

Methods: Six pairs of cadaveric femoral heads were instrumented with a perforated *Proximal Femoral Nail Antirotation* blade. Within each pair, one blade was augmented using 3 ml of polymethylmethacrylate. All specimens underwent cyclic axial loading under physiological conditions. Starting at 1000 N, the load was monotonically increased by 0.1 N/cycle until construct failure occurred. To monitor the migration of the blade, anteroposterior radiographs were taken at 250 cycle increments. Non-parametric test statistics were carried out to calculate correlations and identify differences between study groups.

Results: Inducing failure required a significantly higher number of cycles in the augmented group ($p = 0.028$). Bone mineral density was significantly related with the number of cycles to failure in non-augmented specimens ($p < 0.001$, $R^2 = 0.97$), but not in the augmented group ($p = 0.91$, $R^2 = 0.34$).

Conclusion: Implant augmentation with small amounts of polymethylmethacrylate enhances the cut-out resistance in proximal femoral fractures. Especially in osteoporotic bone, the procedure may improve patient care.

2. Introduction

Recently developed intramedullary implants with new features are increasingly used in the treatment of intertrochanteric hip fractures.[1,2] With the introduction of helical blade designs for improved anchorage in the femoral head, the incidence of cephalic implant cut-out has dropped from approximately 12% [3] to 3.6%.[4] However, in the light of the known demographic pressure and the aging of the population, optimizing fracture fixation remains a priority. Particularly in osteoporotic bone, providing confident and reliable fracture treatment could lead to earlier load bearing and functional recovery with the potential to reduce morbidity and even mortality. The mechanical competence of osteosynthesis depends on a number of factors. In addition to surgery-related issues, such as insufficient reduction or suboptimal implant positioning[5,6,7], bone quality would also appear to be critically important.[8] In older individuals, bone quality tends to be compromised by osteoporosis, a systemic skeletal disease that continues to become more prevalent but also continues to be underestimated and undertreated.[9] Cement augmentation of cephalic hip implants may enhance the implant anchorage, as shown in biomechanical studies.[10,11] The *Proximal Femoral Nail Antirotation* (PFNA, Synthes GmbH, Bettlach, Switzerland) was adapted for additional bone cement application to improve mechanical competence. The PFNA blade is laterally perforated along its axis to enable controlled cement injection through the cannulation of the implant into the cancellous bone structure. Augmentation is performed using a new acrylic cement formulation with medium to high viscosity. The technique allows the surgeon to decide for or against cement augmentation after the implant has been inserted. Until now, we are not able to perform an intra-operative quantitative assessment of the bone quality, but systems that will enable us to perform an intra-operative mechanical assessment of local bone strength are under development (DensiProbe™ AO Research Institute, Davos).

The purpose of this *in vitro* study was to analyse the biomechanical potential of a newly proposed PFNA cement augmentation concept in osteoporotic human specimens.

3. Materials and methods

Six pairs of fresh frozen (-20°C) human cadaveric proximal femurs with low bone density[12] were used in this study, selected out of 15 pairs of femurs from female donors above the age of 80 according to bone mineral density (BMD). BMD was measured by peripheral quantitative computed tomography (pQCT) using an Xtreme-CT (SCANCO Medical AG, Bassersdorf, Switzerland). A cylindrical area of 20 mm diameter and 30 mm length in the center of the femoral head was evaluated, corresponding to the target location of the helical blade and cement cloud.

The six paired samples with the lowest BMD values were included in the study. One femur of each pair was randomly assigned to conventional helical blade fixation, while the contralateral one was treated with a cement-augmented helical blade.

The instrumentation was performed pairwise by an experienced surgeon. Each femur was sawed 50 mm distal to the articular surface, in a plane orthogonal to the planned implant axis. To place a guide-wire in the centre of the femoral head, a custom-made jig was used (Figure 1). The guide-wire was inserted to a depth of 40 mm to avoid perforation of the femoral head. Perforated PFNA blades (PFNA Blade, perforated, length 100 mm, 04.027.035S, Synthes GmbH, Oberdorf, Switzerland; Fig. 2) were inserted over this K-wire without predrilling to a depth of 38 mm. Hence a 12 mm distance was left between the tip of the implant and the apex of the femur corresponding to a tip-apex distance of 24 mm according to the definition of Baumgaertner et al.[5] Subsequently, the guide-wire was removed. In the augmented group, a side opening disposable cannula (Traumacem Needle Kit, Ø 3.3 mm cannula with side-opening, 03.702.120S, Synthes GmbH, Oberdorf, Switzerland; Figure 2) was filled with PMMA bone cement (Vertecem V+, LOT 09CA53010, Synthes GmbH, Oberdorf, Switzerland) with 3 ml syringes (Viscosafe Injection Kit, 07.702.210, Synthes GmbH, Oberdorf, Switzerland) and inserted into the cannulation of the blade to the full depth. Augmentation of the implant with 3 ml of bone cement was performed in a standardized manner with the plunger provided with the cannula system (Traumacem Needle Kit, Ø 3.3 mm Cannula with side-opening, 03.702.120S, Synthes GmbH, Oberdorf, Switzerland); 1 and 0.5 ml etched markings on the plunger provided information on the amount of injected cement. After injection of 1 ml of PMMA through the perforations of the blade into the cranial side of the femoral head, the cannula was turned 180°, allowing caudally directed injection of another 1 ml.

Subsequently, the cannula was withdrawn over 10 mm and the same procedure was repeated by injecting 0.5 ml of PMMA twice.

Mechanical testing was conducted according to the model described by Sommers et al.[13] (Figure 3), simulating an unstable intertrochanteric fracture with a lack of postero-medial support and load sharing at the fracture gap. Implant blade shafts were rigidly mounted to a base fixture at 149º to the vertical plane. This setting reflects a 130º femoral neck angle, a 16º resultant joint load vector to the vertical, plus 3º offset of the femoral shaft axis from the sagittal plane. The femoral heads were mounted on a polymer back plate which rested on two cylindrical rollers, allowing for varus collapse of the head and simulating the characteristics of a reduced unstable intertrochanteric fracture. The blade was free to slide, mimicking full implant dynamic.

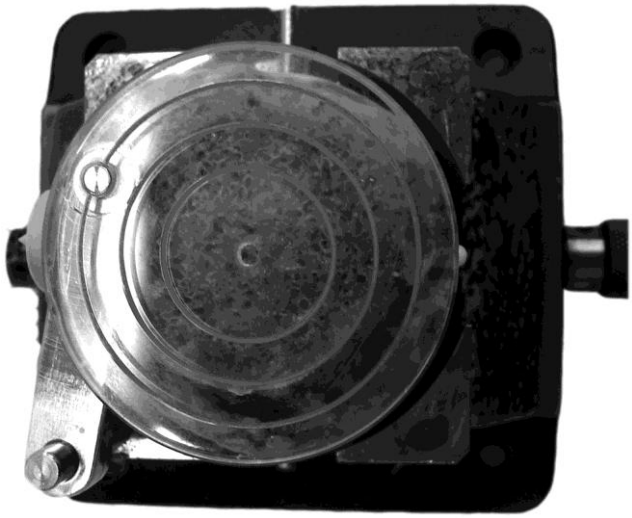

Figure 1

Custom-made jig for guide-wire placement in the centre of the femoral head

Figure 2

Modified PFNA-blade with 12 lateral perforations for cement injection. A disposable side-opening cannula was used for controlled cement application. The cannula was first inserted into the implant cannulation to the full depth to inject 2 ml of bone cement and then withdrawn by 10 mm to inject another 1 ml.

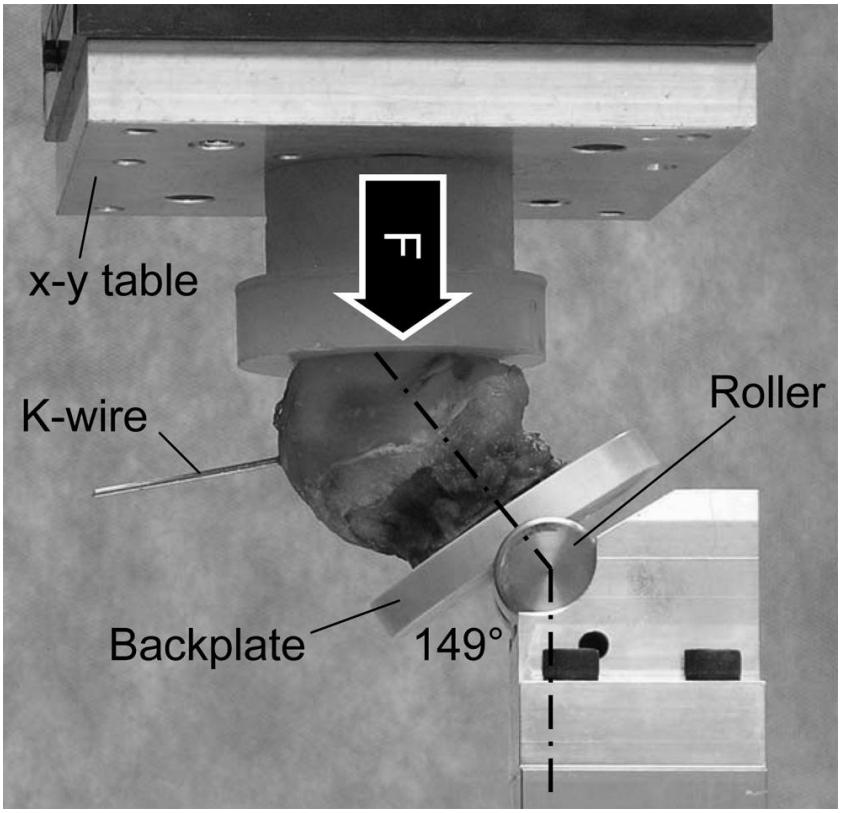

Figure 3

Setup for mechanical testing according to Sommers et al. The sample is free to rotate around the implant axis and can collapse into varus. An x-y table compensates the resulting displacements. A K-wire allows for detection of the head motion. A physiological loading trajectory is transferred to the head in physiological orientation and is cyclically increased until failure of the construct.

Testing was performed on a MTS Mini Bionix II 858 hydraulic test system (MTS Systems Corp., Eden Prairie, USA) equipped with a 4 kN load cell. In order to simulate an alternating load during walking, a loading trajectory resulting from *in-vivo* measurements in the human hip was transferred to the femoral head.[14] Starting at 1000 N the peak load was monotonically increased by 0.1 N/cycle, while the load-valley of the trajectory was maintained at 100 N.[15] Cyclic testing was performed at 2 Hz and was stopped when the displacement of the machine actuator exceeded 10 mm. This value provoked a distinct damage at the bone-implant interface in all cases allowing meaningful retrospective data evaluation.

Data acquisition was performed by radiographic imaging using an image intensifier (Siemens Arcadic Varic, Siemens Medical Solutions AG, Munich, Germany). Anteroposterior radiographs were taken every 250 cycles at the minimum load, to monitor the movement of the head with respect to the blade. The position of the image intensifier was maintained constant throughout the experiment. The varus rotation of the femoral head with respect to the initial X-ray was determined from the radiographs by means of image processing algorithms (Matlab, Mathworks Inc., Natick, USA). A varus collapse of 2°, indicative for loosening of the helical blade, was defined as the point of failure. The number of test-cycles to failure was identified for all specimens. After assessing data distribution (Shapiro-Wilk test), paired non-parametric test statistics (Wilcoxon signed ranks) were carried out to identify differences between groups regarding cycles to failure and BMD. Spearman's correlation coefficient R^2 was calculated for cycles to failure and BMD for both groups. The significance level was set $\alpha = 0.05$.

4. Results

Bone mineral density of the 6 bone pairs was 142 mgHA/cm³ on average, with a standard deviation (SD) of 35. No statistical difference ($p = 0.35$) was found for BMD between groups (non-augmented: 145 mgHA/cm³ (SD 42); augmented: 138 mgHA/cm³ (SD 30)).

The augmented specimens had to be subjected to a significantly higher number of cycles to induce failure ($p = 0.028$). The mean number of cycles to failure was 22,708 (SD 4,411) for the augmented and 15,042 (SD 7,226) for the non-augmented group, respectively (Figure 4). All constructs failed by implant cut-out, resulting in a varus-type collapse of the femoral head (Figure 5). No implant failures were observed during the tests.

The relation between BMD and number of cycles to failure is shown in Figure 6 for both groups. A significant correlation was observed between BMD and the number of cycles to failure for non-augmented specimens ($p < 0.001$, $R^2 = 0.97$). No correlation was found in the augmented group ($p = 0.91$, $R^2 = 0.34$). A significant correlation was observed between BMD and the percentage increase in cycles to failure due to augmentation ($p < 0.001$, $R^2 = 0.99$, non-parametric test). The impact of cement augmentation was inversely related with BMD (Figure 7).

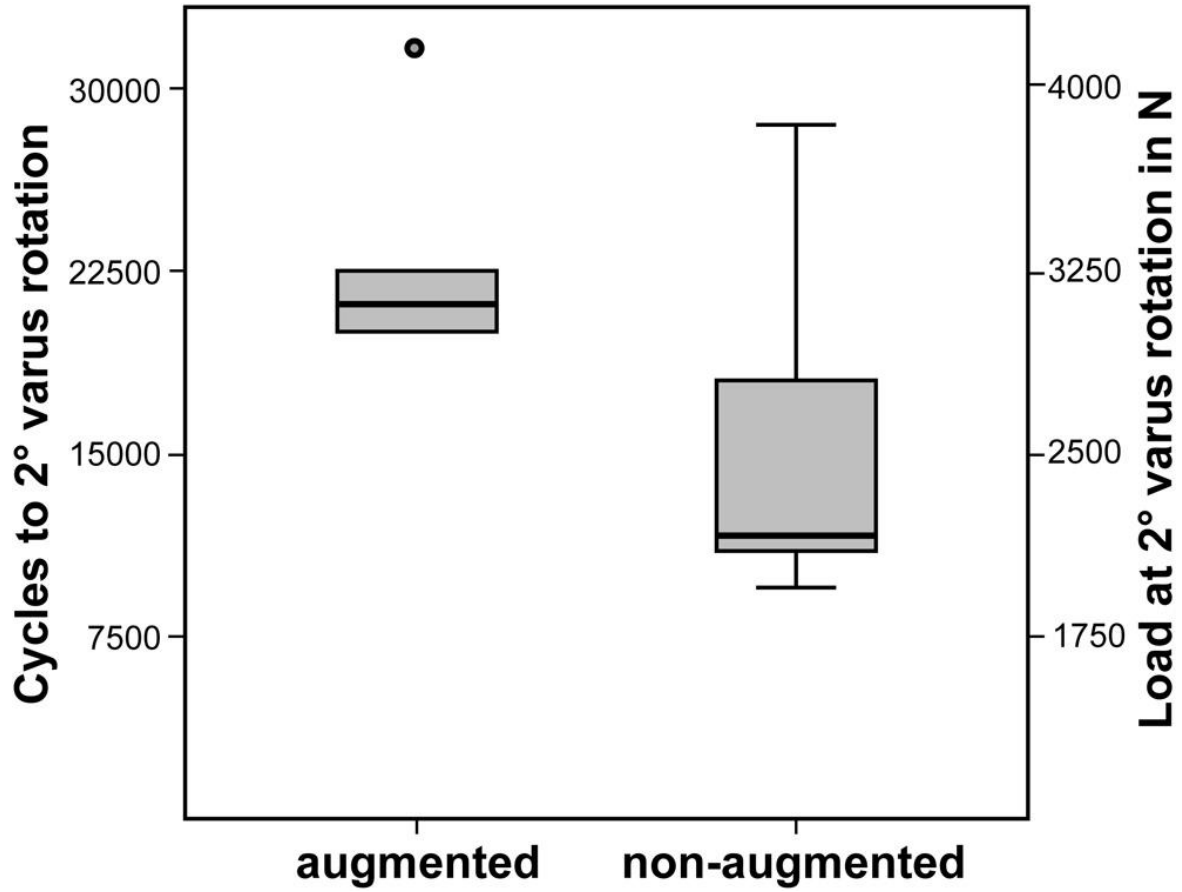

Figure 4

Boxplots of the number of cycles until 2° of varus rotation of the femoral head for both study groups. The augmented samples revealed the highest stability.

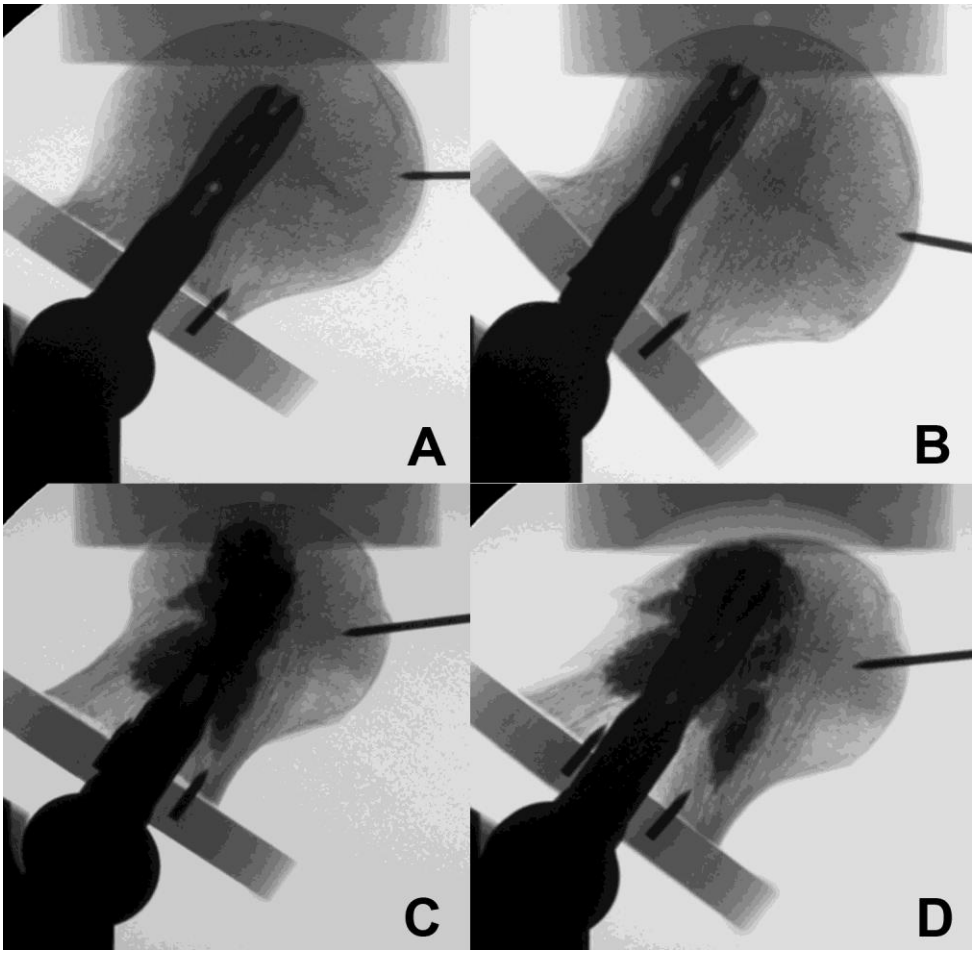

Figure 5

Radiographs of an instrumented non-augmented specimen before (A) and after (B) testing and radiographs of an instrumented augmented specimen before (C) and after (D) testing. After intensive loading, the specimen shows typical varus collapse as clinically seen in the presence of cut-out in both the non-augmented and the augmented case.

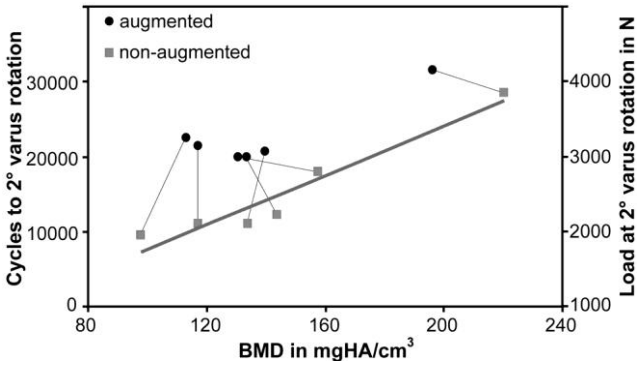

Figure 6

Diagram showing the relation between BMD and number of cycles to failure for both groups. A significant correlation was observed between BMD and the number of cycles to failure for non-augmented specimens ($p < 0.001$, $R^2 = 0.97$). No correlation was found in the augmented group ($p = 0.91$, $R^2 = 0.34$).

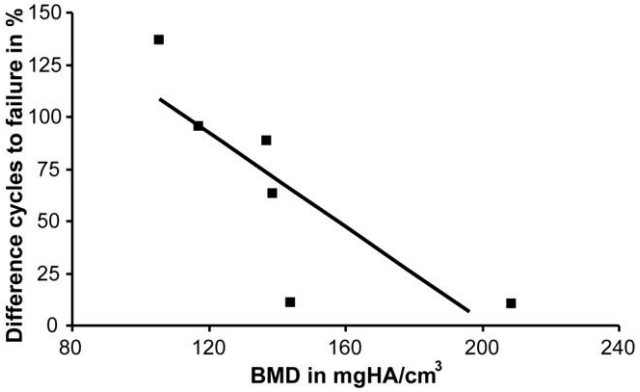

Figure 7

Diagram showing the correlation between BMD and difference in number of cycles to failure. A significant correlation was observed between BMD and the percentage increase in cycles to failure due to augmentation ($p < 0.001$, $R^2 = 0.99$, non-parametric test). The impact of cement augmentation was inversely related with BMD.

5. Discussion

The aim of this study was to compare PMMA augmented helical blades to non-augmented controls in human cadaveric femoral heads. A new augmentation-based implant-set and the corresponding procedure for PFNA were evaluated in a laboratory environment. The results confirmed that even with small amounts of bone cement (in every augmented specimen 3 ml of Polymethylmethacrylate was injected), augmentation significantly improves the implant anchorage in bone of low quality.

In the context of the loading protocol, the constructs, on average, sustained 51% more load-cycles when cement augmentation had been performed. In augmented specimens, no correlation was observed between BMD and cycles to failure, supporting the concept that augmentation rules out the impact of low bone quality and hence reduces the impact of osteoporosis on the implant purchase. On the other hand, the effect of augmentation is reduced with increasing bone quality, suggesting that PMMA augmentation is primarily useful in osteoporotic bone.

Translating the high resolution pQCT measurements to a clinical context needs to be performed with caution, since DEXA (dual energy X-ray absorptiometry) is the predominant method to diagnose osteoporosis. The fact that we used samples from women over the age of 80 – the segment of the population most at risk of osteoporotic fractures – further adds to the clinical relevance of our findings. Other authors[12] measured a representative population of 174 cadaveric femora (median donor age 87) with CT and reported bone mineral densities corresponding to approximately 90 – 290 mgHA/cm³. Hence, our data ranging between 98 – 220 mgHA/cm³ suggests that our samples were representative of the overall elderly population.

Support for potential clinical benefits of implant augmentation comes from both biomechanical and clinical studies. A significant increase in the initial fixation stability of a modified and augmented hip screw compared to a conventional one, has been demonstrated in an intertrochantric fracture model. In agreement with our findings, the most improvement in the context of the lowest bone quality was reported.[10] Another biomechanical study provided evidence for the benefit of hip screw augmentation under cyclic loading, with significantly smaller head displacements and lower failure rates in augmented specimens.[11] In a clinical study, a significantly lower

complication rate in intertrochantric fracture patients treated with cement augmentation, was reported.[16]

Despite supportive evidence, implant augmentation has not achieved a clinical breakthrough yet. Reasons for the rather restrained acceptance of the concept in the medical community may be manifold. One explanation is that, up to now, a standardized technique and a dedicated implant set were missing. In this paper, we present a procedure for PFNA which allows controlled injection of bone cement. Standard instrumentation can be performed with the known biomechanical advantages of blade implants.[17] The lateral perforations of the modified blade implant represent a potential weak point of the implant. Standardized material testing of the implants, as performed by the manufacturer in beforehand, revealed no increased risk for implant failure due to the perforations. Furthermore our tests did not reflect any failure of the implant itself. If required, the anchorage may be further enhanced by additional cement augmentation. In our study, this was done according to a defined protocol. Compared to previously reported augmentation techniques, possible devastating complications can be avoided by including careful adaptations to this protocol, of which avoidance of femoral head perforation, the use of a limited amount of PMMA and localization of the PMMA around the implant are the most important.

In the current clinical workflow, feedback during surgery is essentially based on subjective judgment by the surgeon. Most hip fracture patients do not undergo DEXA or CT measurement. However, to prevent unnecessary cement injection, a quantitative assessment of the bone quality might be useful, since cement augmentation seems to be most effective in osteoporotic bone. Mechanical assessment of local bone strength might be an alternative. In fact, in a number of biomechanical experiments, measuring the breakaway torque of the local trabecular structure (DensiProbe^{TM} AO Research Institute, Davos) during surgery has been proven to reliably predict implant cut-out at different anatomical regions.[18] Application of this concept to the hip is currently investigated in a clinical multicenter trial and may ultimately be included in the PFNA implantation-set as a next step.

When using cement injection, extravasation of non-biodegradable bone cement into the hip joint might have devastating consequences. A perforation of the K-wire through the femoral head should therefore be avoided. In cadaver experiments and

in *in vivo* trials, preserved cortical and cartilage layers were verified by injection of Iopramida contrast agent (Ultravist 300, Schering AG, Zürich, Switzerland) prior to cement application. When leakage of the contrast agent is identified by radiography, augmentation should be strictly avoided. One strategy to reduce the risk of cement leakage, is to use a new type of PMMA cement with a medium to high viscosity[19]. In our cadaver experiments, it seemed that the required injection pressure increased with increasing BMD. In fact, in some of our pilot specimens with higher bone density values, it was not even possible to manually inject cement into the bone structure. In some experiments, we recognized a scattered, uneven distribution of the PMMA along the blade axis in spite of a standardized augmentation technique (Fig. 5), with PMMA accumulating at the tip or at the base of the helical blade or at the cranial or caudal site, respectively. In addition to inhomogeneities of the bone structure, cancellous bone compaction as a result of implant insertion[15] might impede or redirect the cement flow towards a certain region. However, the relevance of these issues from a clinical perspective remains to be clarified. Nevertheless, from a biomechanical perspective, it would seem that the cement should be concentrated at the implant tip and that radiographic monitoring of cement distribution is recommended. Baumgaertner et al.[5] already expressed the importance of the tip-apex distance as key-factor for a successful component outcome. Mechanically, reducing the distance between implant tip and apex reduces the lever-arm of the hip joint contact force and hence diminishes the stresses in the bone structure. Accentuated presence of bone cement at the tip might therefore be beneficial from a biomechanical perspective. The individual roles of several key factors, such as cement location, amount of cement, tip-apex distance, with regard to the implant anchorage is still unclear and will be the subject of future experiments.

Potential drawbacks of PMMA augmentation such as cement leakage, fat emboli, toxicity, thermal effects and devascularisation are directly related to cement volume and distribution.[20] Contrary to studies performed by pioneers in PMMA application for the treatment of unstable intertrochanteric hip fractures[21], we used comparatively small amounts of bone cement (3 ml) to minimize impact on the biological environment. The risks of cement leakage and fat emboli have been evaluated in vertebroplasty related studies, where in an extreme case of multiple level augmentation total cement volumes of up to 25 ml have been advocated as safe[22]

but this should also be evaluated in the hip joint. In addition to cement volume, heat generation may have safety implications as well. One of the concerns with heat generation due to exothermic polymerization is osteocyte necrosis. According to a previously performed *ex vivo* study[23], the used cement volume of 3 ml may not affect bone sensitivity to thermal destruction. Finally, it should be noted that chondrocytes might be more sensitive to the deleterious effects of PMMA than osteocytes. Therefore, any subchondral localization of bone cement should be avoided.[24] The absence of temperature monitoring at the surface of the femoral head during the application of PMMA, can be considered as a first limitation of this study. Besides this, some other limitations need to be mentioned. First of all, only one mode of failure (varus collapse and cut-out of the helical blade) was tested, whereas other modes of failure like backing-out of the helical blade and non-sliding of the system have been mentioned in clinics. Secondly, only uni-axial loading was tested while multiplanar loading, more suggestive to normal gait, was not tested. In our experiments, a suboptimal implant position was chosen as represented by a rather large tip-apex distance (24 mm according to Baumgaertner et al.). This configuration created a worst-case scenario and provoked clinical failure even in specimens with healthy bone stock. However, clinically a reduced tip-apex distance is recommended.
With regard to implant removal, our tests in the laboratory did not reveal any difficulties to withdraw the blade from the cement volume. A layer of fat and bone marrow between implant and cement might prevent bonding of the materials. In the unlikely event of a revision osteosynthesis, where arthroplasty would normally be the operation of choice, it was already suggested to power drill and tap PMMA cement.
Some of the abovementioned risks and dangers are related to the nature of acrylic based biomaterials. Biodegradable bone cements, e.g. those based on calcium phosphates, are upcoming. Possible advantages are disintegration of leaked cement, the absence of an exothermal reaction and the feasibility of revision operations.[25] Nevertheless, inferior biomechanical properties disqualify currently available biodegradable alternatives for the indented use.[11] Moreover, their disappearance over time due to resorption questions the application in old and frail patients in whom avoidance of fixation failure and refracturing are of utmost importance.

6. Conclusion

This *ex vivo* study shows that implant augmentation with small amounts of bone cement significantly enhances the cut-out resistance in proximal femur fractures treated with a modified PFNA. The procedure is primarily indicated for osteoporotic bone and appears to be a valuable treatment option with clinical benefits in the elderly that seem to outweigh any possible risks associated with implant augmentation.

7. Acknowledgment

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Chapter V

Cement augmentation of hip implants in osteoporotic bone: how much cement is needed and where should it go?

This chapter has been published as:
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1. Abstract

Purpose: Several studies have proven the beneficial effect of cement augmentation of Proximal Femoral Nail Antirotation (PFNA) blades on implant purchase in osteoporotic bone. It is the purpose of this in vitro study to investigate the effect of different localisations and amounts of bone cement.

Methods: Polyurethane foam specimens were instrumented with a PFNA blade and subsequently augmented with polymethylmethacrylate (PMMA) bone cement. Eight study groups were formed based on localisation and amount of cement volume related to the blade. All specimens underwent cyclic loading with physiological orientation of the force vector until construct failure. Foam groups were compared between each other and to a cadaveric control group.

Results: The experiments revealed a significant dependency of implant purchase on localisation and amount of cement used. Biomechanically favourable cement positions were found at the implant tip and at the cranial side. However, none of the tested augmentation patterns performed significantly inferior to the cadaveric benchmark.

Conclusion: In an experimental test setting, localisation and amount of cement influenced the biomechanical competence of augmented PFNA blades in simulated porous cancellous bone. These findings will allow surgeons to further reduce the amount of injected PMMA, decreasing the risk of cement leakage or cartilage damage.

2. Introduction

With the use of novel fixation devices like helical blades for the treatment of proximal femoral fractures, the incidence of cut-out of cephalic implants has decreased importantly.[1-5] Nevertheless failures do occur. Besides surgeon related factors such as the quality of the reduction and the positioning of the implant, the bone quality plays an important role in the occurrence of devastating mechanical complications.[6,7]

Due to the aging of our population and the relatively poor compliance to drugs that prevent osteoporotic fractures, the incidence of osteoporosis related fractures will increase.[8]

The technique of implant augmentation is based on an increasing congruence between the implant and the bone thereby reducing the stresses developed at the implant to bone interface.[9,10] A biomechanical study on augmentation of conventional hip screws showed beneficial results in osteoporotic cadaveric bones.[11] Subsequently, implant augmentation was performed through a cannulated and perforated implant. In several in vitro studies, cement augmentation of Proximal Femoral Nail Antirotational blades (PFNA, Synthes GmbH, Bettlach, Switzerland) has been proven to be clearly beneficial in terms of biomechanical performance in osteoporotic bone.[12-14] Recently, the first clinical results of PFNA helical blade augmentation were published.[15]

However, both in vitro and in vivo studies revealed a considerable variation of cement distribution around the implant when using at least 3 ml PMMA. Accurate positioning of the cement seems difficult to achieve. The exact role of localisation and cement volume on the implant purchase is unclear. Determination of an optimal localisation and volume for the cement could reduce the risk of several hazards accompanying cement application, such as cement leakage or adverse effects on the cartilage.[16]

The objective of this experimental study was to systematically investigate the effect of localisation and amount of PMMA cement on the mechanical competence of PFNA proximal femur constructs under cyclic loading. We wanted to determine the position and the amount of bone cement needed to achieve sufficient implant purchase in the osteoporotic femoral head with minimal alteration of the biological system.

3. Methods

3.1. Study-groups

36 surrogate foam specimens with defined geometry were used as model for human cancellous bone (Figure 1). The specimens consist of cellular polyurethane foam (10 pcf, 1522-10, Pacific Research Inc., Malmö, Sweden) representing human cancellous bone. We used a density of 10 pcf (pounds per cubic foot, 160.2 kg/m³) to simulate an osteopenic bone structure.[13,17] These samples were divided into six study groups (n = 6) with different amounts and localisations of cement with respect to the blade (groups 1-6, Figure 2, Table 1). From a previous study with similar settings, the mechanical test raw data from a group with concentric distribution of 3 ml PMMA at the tip of the blade (n = 6) and a non-augmented control group (n = 6) were re-evaluated to fit the failure criterion of the present study of 2° of varus collapse and integrated in the present study (groups 7-8).[13] Additionally, two reference groups were established from 12 fresh-frozen human cadaveric femoral heads. These reference groups were accomplished by adding the re-evaluated mechanical test raw data of the 6 non-augmented cadaveric femoral heads of a former study[14] to the mechanical test raw data of 6 cadaveric femoral heads instrumented with a helical blade without augmentation for the present study. The cadaveric femoral heads consisted of 4 right and 8 left bones, 8 females and 4 unknown at a mean age of 87.2 ± 5.2 years (mean ± SD) with a range between 81 and 96 years. Specimens were obtained from the Department of Pathology, Kantonspital Basel, Switzerland, with appropriate consent of the relatives.

Prior to testing, all human specimens underwent bone mineral density (BMD) measurements in the cancellous bone with peripheral quantitative computed tomography (pQCT) using an Xtreme-CT (SCANCO Medical AG, Bassersdorf, Switzerland). According to the mechanical testing results, the specimens were retrospectively divided into "weak" and "strong" cadaveric groups (groups 9-10, n = 6, see *Data acquisition and evaluation*).

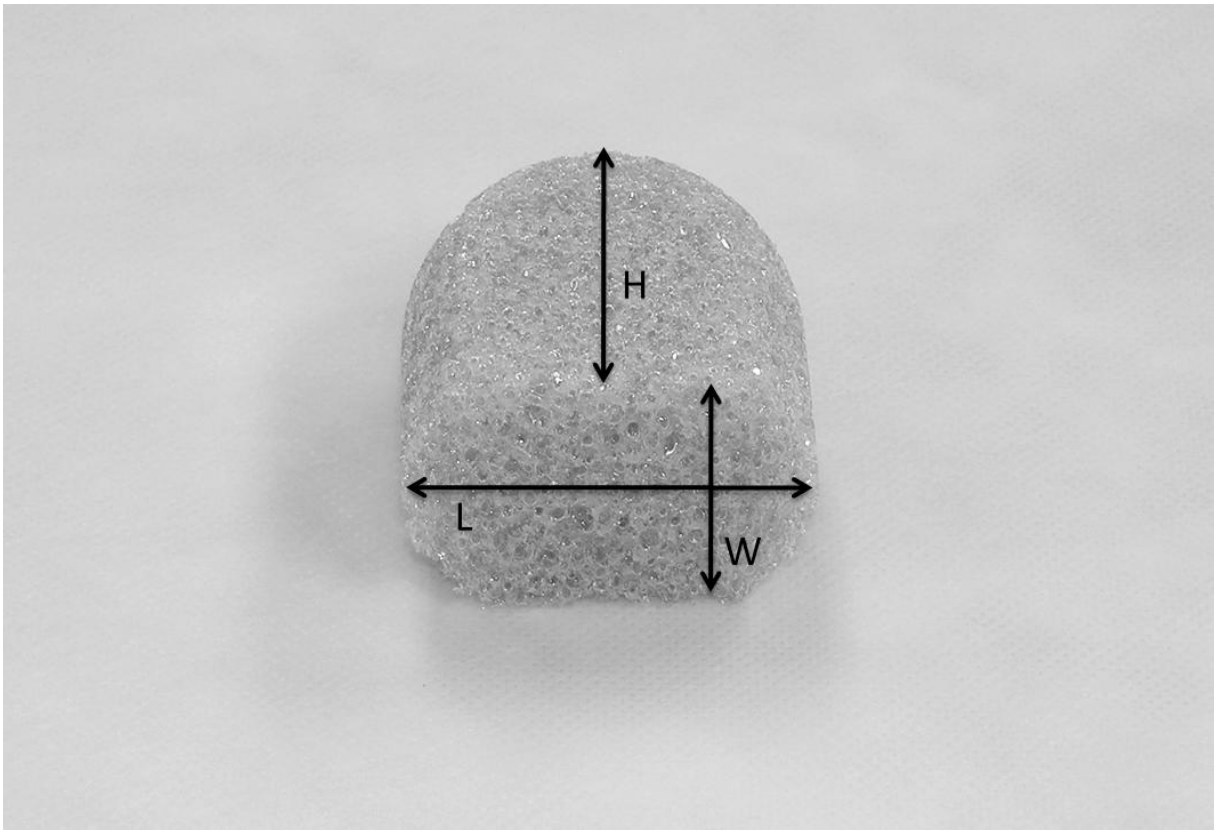

Figure 1: Foam specimen

Polyurethane foam block to simulate porous cancellous bone in the femoral head machined to fit into a custom-made polymer shell for mechanical testing. Height (H) = 50mm, length (L) = 50mm, width (W) = 38mm.

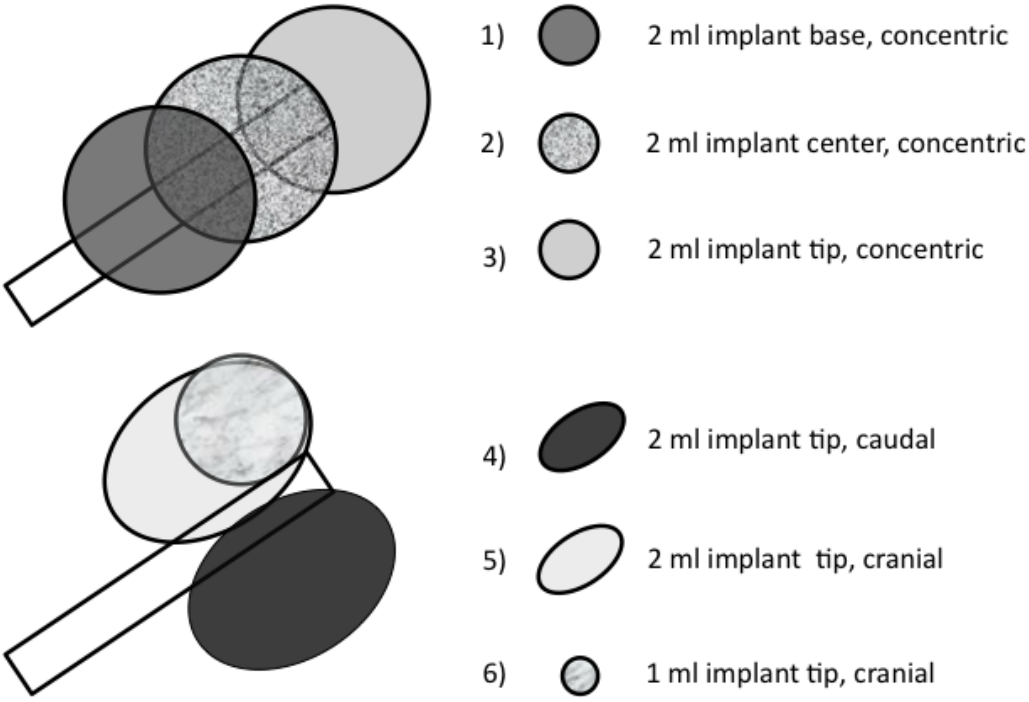

Figure 2: Schematic illustration of the tested augmentation patterns

Top: Concentric distribution of 2 ml bone cement at the PFNA blade base, centre and tip.
Bottom: Caudal and cranial placement of a 2 ml cement cloud and a 1 ml cranial cloud.

Group	Specimens	Cement volume	Cement location axial	Cement location transverse
1	Foam	2 ml	implant base	concentric
2	Foam	2 ml	implant center	concentric
3	Foam	2 ml	implant tip	concentric
4	Foam	2 ml	implant tip	caudal
5	Foam	2 ml	implant tip	cranial
6	Foam	1 ml	implant tip	cranial
7	Foam*	3 ml	implant tip	concentric
8	Foam*	--	--	--
9	Human bone "weak"	--	--	--
10	Human bone "strong"	--	--	--

Table 1: Study-groups

Groups 1-8 consist of polyurethane foam samples for testing of different amounts and localisations of bone cement. Group 8 represents a non-augmented control. * indicates groups from a different study[13]. Groups 9 and 10: human cadaveric references. Group-size n = 6.

3.2. Instrumentation

The foam specimens were placed in a custom-made polymer shell to mimic the cortex of the femoral head for subsequent load introduction. A special jig was used to introduce a 3.5-mm guide-wire in the center of the foam. Perforated PFNA-blades (length 100 mm, Synthes GmbH, Bettlach, Switzerland, Figure 3a) were inserted over the guide-wire without predrilling to a depth of 38 mm, resulting in a 12 mm distance between the implant tip and the apex of the foam. According to the definition of Baumgartner et al.[18], this led to a suboptimal tip-apex distance of 24 mm to provoke failure as seen in clinics.

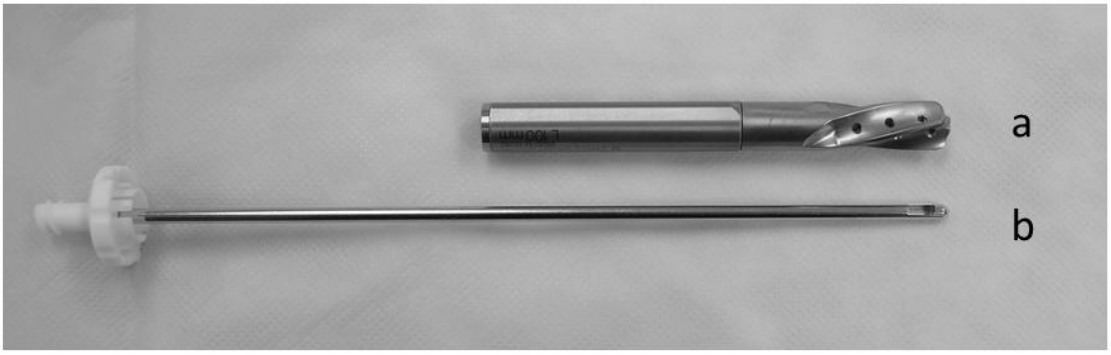

Figure 3: Instrumentation of foam specimens
3a: Perforated PFNA blade (Synthes GmbH)
3b: Side-opening cannula to inject bone-cement through the perforated blades

Subsequently, cement augmentation was performed through the cannulation of the blades for each study group following a standardized technique. In all augmented groups, the guide-wire was removed and a side opening cannula (Vertebroplasty Needle Kit, 8 Ga, Article number: 03.702.216S, Synthes GmbH, Oberdorf, Switzerland) (Figure 3b) was prefilled with PMMA bone-cement (Vertecem V+, Synthes GmbH, Oberdorf, Switzerland). Thereafter, 2 ml (groups 1-5) or 1 ml (group 6) of PMMA was injected through the perforations of the blade into the foam specimens by using 1 ml syringes (Traumacem V+ Syringe Kit, Article number: 03.702.130S, Synthes GmbH, Oberdorf, Switzerland). In groups 1-3, 2 ml of PMMA was concentrically distributed around the blade's base (group 1), center (group 2) or tip (group 3) by injecting 1 ml of PMMA to the cranial side, turning the cannula by 180° and injecting another 1 ml of PMMA to the caudal side.

The cannula was either completely inserted (group 3) and subsequently withdrawn by 7 mm (group 2) or by 12 mm (group 1) to position the cement at the respective localisation along the blade axis. In group 4, a total of 2 ml PMMA was placed at the caudal side of the blade by inserting the cannula completely, injecting 1 ml of PMMA to the caudal side, withdrawing the cannula by 7 mm without turning it and injecting another 1 ml to the caudal side. In group 5, a total of 2 ml of PMMA was placed at the cranial side of the blade by inserting the cannula completely, injecting 1 ml of PMMA to the cranial side, withdrawing the cannula by 7 mm without turning it and injecting another 1 ml to the cranial side. In group 6, 1 ml of PMMA was injected to the cranial side of the blade after inserting the cannula completely into the cannulation of the blade (Figure 2).

By prefilling the cannula with cement and by inserting it deep enough to enable the side opening to directly reach the perforations of the blade in all study groups, the exact amount of PMMA injected into the bone model was known. Because the polyurethane foam model allows for a well-controlled cement distribution[13], a consistent cement configuration could be obtained for each of the study groups (Figure 4).

Human specimens were instrumented according to a recently published protocol[14] according to the procedure described above without augmentation and without using the polymer shell.

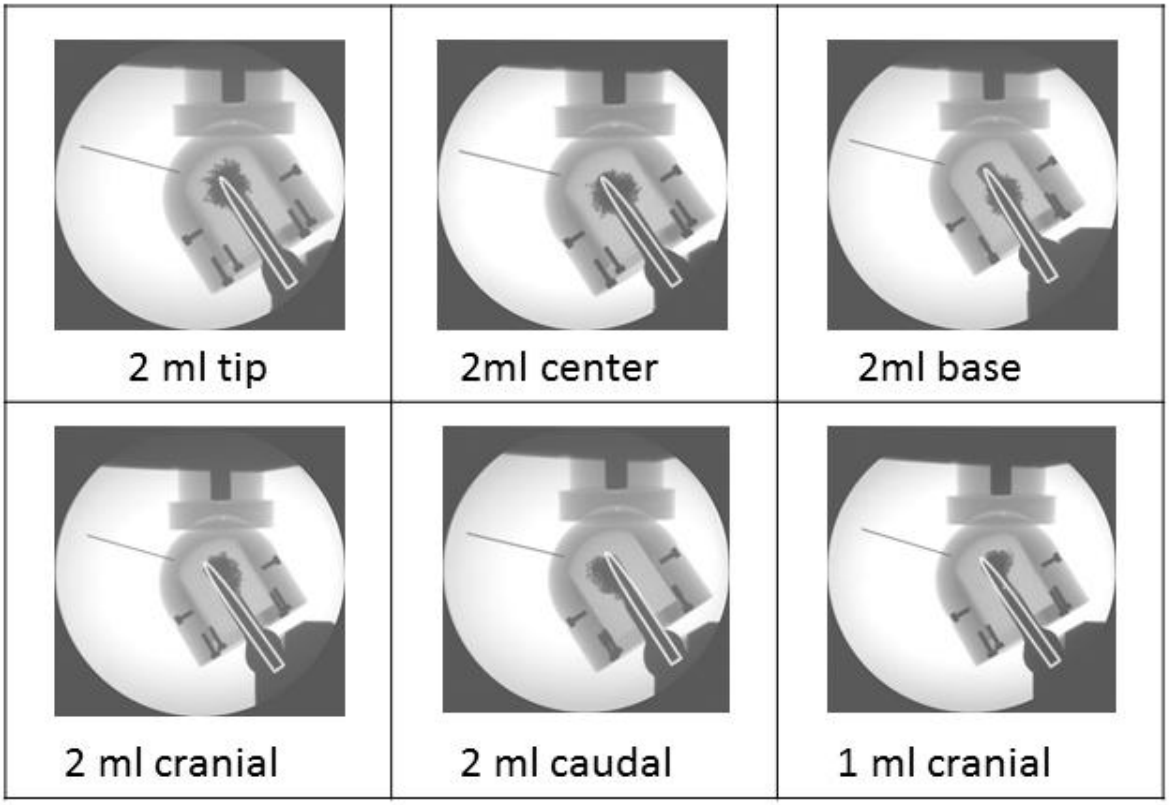

Figure 4: Overview of cement configurations for each of the study groups

3.3. Mechanical testing

The testing model, initially described by Sommers et al.[19] and further adapted in our recent studies,[13,14] simulating an unstable intertrochanteric fracture, was also used in this experiment. The setup allows the head component to rotate into varus, while the blade migrates through the foam structure. The polyurethane foam samples were placed in a plastic shell for load introduction.

Testing was performed on a servo-hydraulic testing machine (model 858, Mini Bionix; MTS, Eden Prairie, USA) equipped with a 25 kN load cell. The force progression in the human hip during normal gait as provided by Bergmann et al.[20] was cyclically transferred to the specimen in physiological orientation of the load vector[13], simulating an alternating load during walking. In order to achieve a 16° resultant load vector to the vertical, a 130° femoral neck angle, and a 3° offset of the femoral shaft axis from the sagittal plane, the implant shaft was mounted to a base fixture at 149° to the horizontal free to slide along its axis (Figure 5). A cross-table was used to eliminate parasitic forces during testing. Starting at 1000 N the load was monotonically increased by 0.1 N/cycle until failure of the construct according to the protocol of Windolf et al.[21] The load-valley was maintained at 100 N throughout the test. Cyclic testing was performed at 2 Hz.

Testing was stopped when the crosshead displacement exceeded 8 mm. Failure occurred at the implant to bone or cement to bone interface depending on the localisation of the PMMA and was determined by analysis of the X-Rays that were performed throughout the test (for details on X-Ray monitoring: see "*Data acquisition and evaluation"* section).

Human specimens were cyclically tested in a similar manner according to a recently published protocol.[14] Load was not introduced via the polymer shell but directly transferred to the head using a moulded cup.

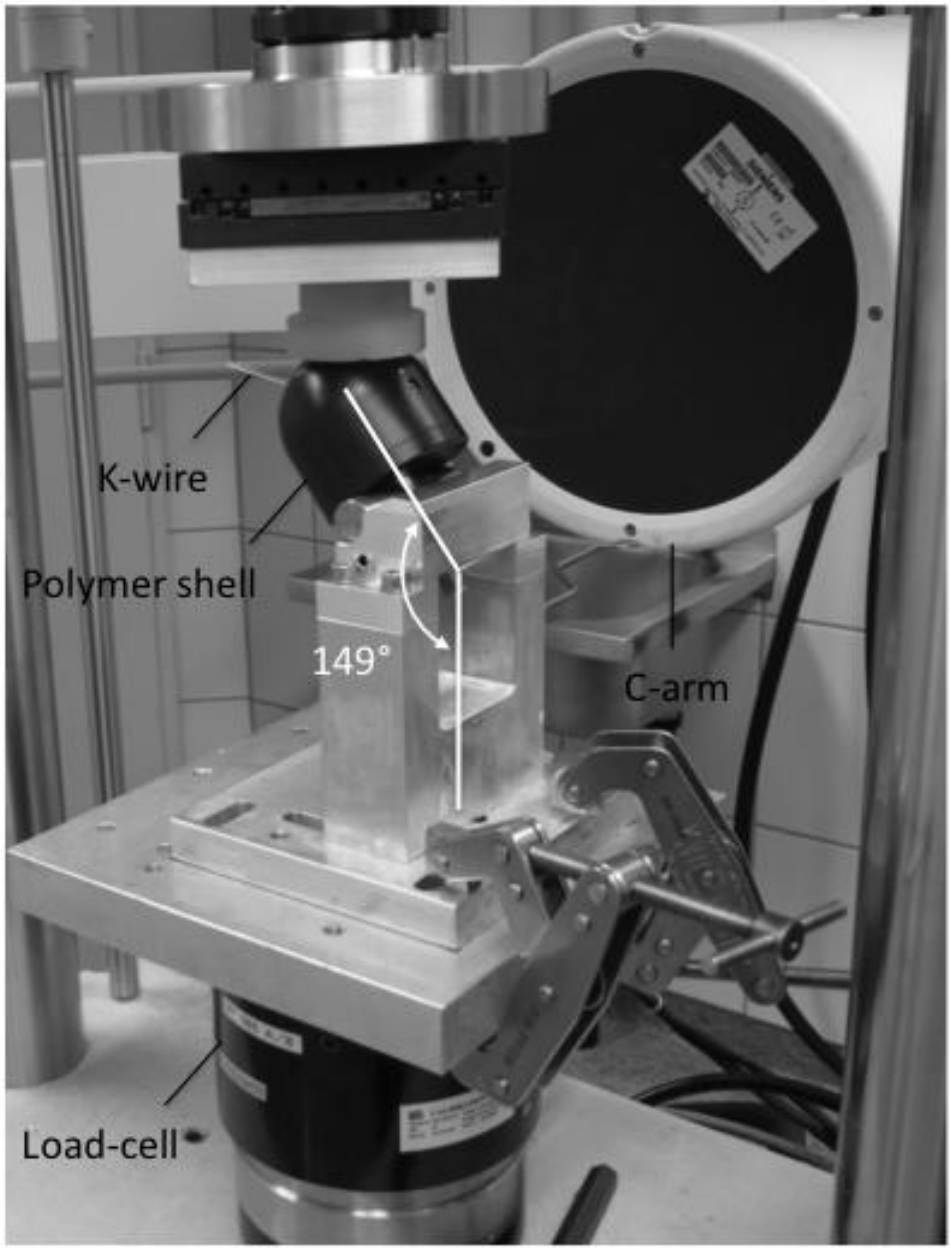

Figure 5: Test setup

Foam specimen on testing machine. Loading is cyclically introduced to the polymer shell under physiologic orientation. Varus rotation of the sample is monitored by periodic X-rays. A K-wire attached to the shell acts as marker for X-rays evaluation.

3.4. Data acquisition and evaluation

A K-wire was connected to the polymer shell / human femoral head in the mediolateral plane to monitor progression of varus rotation of the specimens from radiologic images during testing. A C-arm (Arcadis Varic, Siemens Medical Solutions AG, Munich, Germany) was positioned in anteroposterior direction. Radiographs were taken every 250 cycles at minimum load (100 N) to monitor the plastic varus deformation of the test specimens in relation to the blade. The change in angulation of the K-wire with respect to the initial X-ray was determined from the radiographs by means of image processing algorithms (Matlab, Mathworks Inc., Natick, USA).

Retrospectively, a varus collapse of 2° was defined as the point of failure.[13,14] This failure criterion is a pure varus rotation as all other movements (translation, torsion around the blade axis) were eliminated by the design of the test fixture and cannot occur. Implant bending was not observed in any of the tested specimen. The number of test-cycles to failure was identified for all specimens.

The radiographs were further analyzed to identify the distance of the center of the PMMA volume to the apex of the foam sample for group 1 (blade base), group 2 (blade center) and group 3 (blade tip). The centroid of the projected cement volume was estimated by fitting an ellipse to the cement contour. The six human specimens having survived most cycles until 2° varus collapse occurred formed the "strong" cadaveric reference group, whereas the remaining six specimens were allocated to the "weak" cadaveric group.

3.5. Statistics

Shapiro-Wilk tests served as decision criterion for the appropriate test statistics. All study-groups were compared with respect to number of cycles to 2° varus rotation employing a univariate ANOVA (analysis of variance) with Bonferroni post-hoc correction for multiple comparisons. Additionally, Pearson’s correlation coefficient R was calculated for cycles to failure and localisation of the PMMA volume along the implant axis by pooling study-groups 1, 2 and 3. BMD of the "weak" and "strong" cadaveric specimens were compared using a t-test. The significance level was set to $\alpha = 0.05$.

4. Results

The performances of all study groups are illustrated in Figure 6. The number of cycles to failure for each study group is mentioned in the according bar as follows: mean ± standard deviation. Regardless the augmentation pattern, all augmented foam samples survived significantly longer than the non-augmented foam group (group 8, all $p < 0.001$). However, there was a clear influence of the augmentation pattern on the mechanical competence of the construct. The best performance was seen in the 3 ml group (group 7) with 253% increase in cycles to failure compared to the non-augmented control.

However, the performance of this group was not significantly different to 2 ml cranial cement placement at the implant tip (group 5, $p > 0.99$). The least competent augmentation pattern was 2 ml cement at the implant base (group 1) leading to 99% increase in cycles to failure compared to the non-augmented control. However, there were no statistical differences between the latter group and 2 ml caudal placement at the implant tip (group 4, $p > 0.99$) or 1 ml cranial placement at the tip (group 6, $p > 0.99$). 2 ml cranial cement placement (group 5) was significantly superior to 2 ml cement at the caudal side (group 4, $p < 0.001$). 2 ml cranial cement (group 5) was also superior to 1 ml cranial cement (group 6, $p = 0.001$).

The distance of the centre of the PMMA volume to the apex of the foam correlated inversely with the number of cycles to failure ($R = 0.77$, $p < 0.001$).

Bone mineral density of the "weak" and "strong" cadaveric groups (groups 9 and 10) was 143 ± 35 mgHA/cm^3 and 195 ± 33 mgHA/cm^3 (mean ± SD), respectively. This difference was significant ($p = 0.023$). Cycles to failure of the "weak" cadaveric group (group 9) were not statistically different to the non-augmented foam group (group 8, $p > 0.99$). Cycles to failure of the "strong" cadaveric group (group 10) were not significantly different to the augmented foam groups (all $p > 0.99$). Exceptions were 2 ml cranial cement placement at the tip (group 5) and 3 ml cement at the tip (group 7), which both performed superior to the “strong” cadaveric group (both $p < 0.009$).

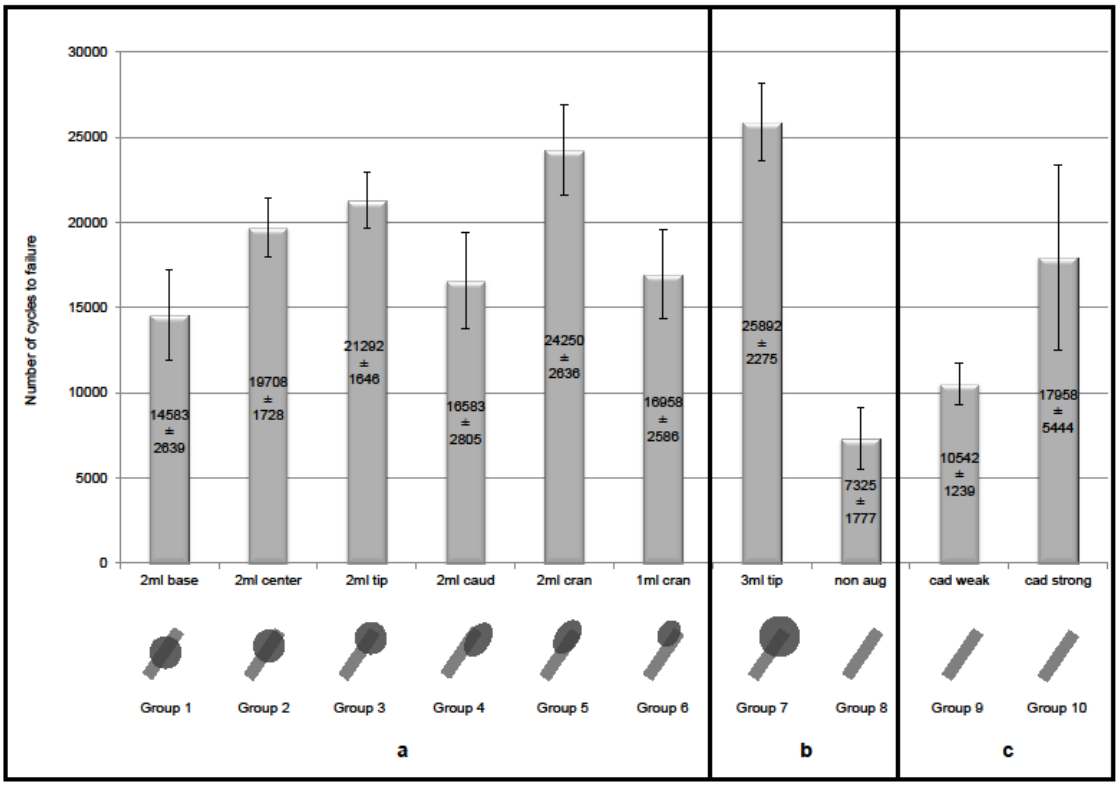

Figure 6: Performance of study groups

The number of cycles to failure for each study group is mentioned in the according bar as follows: mean ± standard deviation.

6a: Number of cycles to failure of the 6 foam groups (groups 1 to 6).

6b: Number of cycles to failure of an augmented foam group with concentric distribution of 3 ml of PMMA at the blade tip (group 7) compared to a non-augmented foam-group (group 8) obtained from re-evaluation of the mechanical test raw data of a former study. [13]

6c: Human cadaveric reference groups (groups 9/10) obtained from the testing of 6 human cadaveric femoral heads that were instrumented with a helical blade without augmentation for the present study and the re-evaluation of the mechanical test raw data of the 6 non-augmented cadaveric femoral heads of a former study.[14]

Bars represent mean ± standard deviation of 6 specimens.

5. Discussion

The technique of cement augmentation of PFNA blades for enhanced fracture fixation in porous bone already showed promising results in several biomechanical studies. A first study, performed on foam models mimicking osteoporotic bones, showed a beneficial effect of augmentation on implant stability by an increased cut-out resistance.[13] Two other studies, performed on osteoporotic cadaveric bones, showed an increased rotational stability, pull-out resistance and cut-out resistance of augmented bones compared to a non-augmented control group.[12,14]

A first clinical study on the use of PFNA augmentation also shows promising radiological and functional results without major intra-operative complications.[15]

Nowadays, augmentation of the femoral head through a cannulated and perforated PFNA blade is gaining acceptance amongst surgeons. By using a side-opening cannula for cement application it is aimed to selectively position the cement at the tip of the helical blade. The risk of cement leakage into the fracture site[16, 23-26] or at the level of the sliding mechanism of the nail is thereby reduced. Cement leakage into the hip joint through a perforation of the femoral head, frequently created during guide-wire placement, can be excluded by performing a leakage test prior to augmentation.[15] However, clinical and experimental experience shows that controlled positioning of the cement volume inside the bone is not always possible.[14,15] Cement follows the path of least resistance and cannot always be sufficiently directed by the injection procedure. The question arises to which extent an unfavourable cement localisation can compromise the desired biomechanical benefits. Moreover it is unclear to which extent the amount of cement can be reduced to exclude potential complications such as leakage or thermal necrosis.[16, 23, 26, 28]

This in vitro study compared selected cement amounts and patterns along and transverse to the PFNA blade axis in a foam model. An overview of the various cement configurations is shown in figure 4. It is clear that the cement distributions in foam are not fully comparable to the distributions in human bone. The questions how and why certain cement distributions in human bone occur, belong to a separate topic and are beyond the scope of this study. Foam was used in our experiments for sake of reproducibility of cement patterns. This allowed us to investigate the mechanical consequences of specific cement localizations. A clear effect on implant purchase of both, localization and amount of PMMA became obvious. The

biomechanical competence of the construct increases with placing the cement towards the tip of the implant. This finding can be explained by the lever-arm principle. A longer lever to the hip joint contact force generates higher moments acting on the anchoring point of the implant. Reducing the lever creates a biomechanically superior situation. In a clinical context this basic principle was already stated by Baumgartner et al.[18] stressing the importance of the tip-apex distance for hip fracture fixation. On the other hand, care should be taken from a biological point of view not to inject the PMMA too close to the subchondral area to avoid potential cartilage damage.[29] Concerning the influence of PMMA localisation transverse to the blade axis, this study showed that a caudal localisation of PMMA in relation to the blade is biomechanically inferior compared to cranial or concentric position.

This appears intuitive since physiological loading is dominated by compression and PMMA based bone cements provide superior performance under compression than tension. From a handling perspective it might be easier to create a concentric cement volume. From a biomechanical point of view, however, cement placed cranial to the implant tip seems most promising.

When considering the amount of PMMA in addition to the localisation, this study showed that a cranial localisation of 2 ml of PMMA is comparable to a concentric localisation of 3 ml around the blade tip. Furthermore, a 1 ml cranial cement placement revealed comparable resistance against cut-out as a 2 ml caudal cement position. Provided that reliable augmentation of biomechanical superior bone regions becomes possible, the volume of cement could hypothetically be reduced to 1 ml.

For clinical interpretation of our findings a comparison with data from non-osteoporotic human bone was necessary. In general, the aim of augmentation is to rule out the influence of osteoporosis by enhancing the purchase of implants to a level similar to healthy bone. From a group of 12 cadaveric samples the six best performing specimens were selected to form a "healthy" reference group. Rather than clustering the cadaveric samples according to BMD, grouping into "weak" and "strong" was performed according to cycles to failure because the target parameter of the study was mechanical bone strength and not mineral density.

When comparing the average BMD of the "strong" or "healthy" group (~200 mgHA/cm^3) to the literature (BMD range approx. 90-290 mgHA/cm^3, 174 specimens)

this appears to be a reasonable assumption.[30] All augmented study-groups performed as well or better than the non-augmented cadaveric benchmark, suggesting that even unfavourable augmentation patterns can provide a sufficient biomechanical benefit. This implicates that clinical difficulties with cement positioning might be of minor importance. From another perspective, the use of 3 ml of bone cement at the tip of the PFNA blade could even be considered too much.

It has to be emphasised that these are all theoretical considerations and there are some limitations associated with the study. Polyurethane foam can only resemble human cancellous bone in a restricted way. However, the approach is still powerful, since the homogeneity of a synthetic material offers reproducibility of tests which is impossible to achieve with biological bone samples. The foam material was successfully used in a previous study[13] and compared to a group of human bone samples with low bone mass (average BMD 143 mgHA/cm^3). No statistical difference was found between non-augmented foam and human bone under cyclic loading, supporting the similarity between the synthetic material and human bone. In the actual study, a group of 12 cadaveric human femoral heads was used to create a benchmark of 6 “healthy” bones. On a mechanical base, the 6 weaker specimens were discarded to come closer to a “healthy benchmark” than when using all 12. Especially when taking into consideration the mean age of the donors (87.2 years), it is quite likely that not all were in healthy shape. However, defining the exact value of benchmarks of human cadaveric bones requires a separate study what is beyond the scope of this work.

Furthermore, care should be taken when applying the results of our study to the clinical situation. It remains difficult to control the localisation of PMMA around implants in human bones. Thus, radiographic monitoring of the cement distribution during augmentation is crucial. Subchondral localisation or leakage must be avoided and the procedure should be stopped as soon as cement flows into undesired directions. New methods or instruments for controlling/predicting the cement flow during injection are needed to increase the procedural security. PMMA formulations have evolved in terms of viscosity and curing window, but they can be further optimized. These findings stress the promising and challenging aspects of implant augmentation in osteoporotic bone.

6. Conclusion

In this study, we could show that the mechanical competences of all groups of augmented specimens are comparable to the mechanical competences of non-osteoporotic cadaveric bones, independently of the augmentation pattern or the amount of PMMA used. Given the fact that in clinical practice control of PMMA distribution is not always possible, this finding implicates that even in an unfavourable localisation from a biomechanical point of view, augmentation is still better than no augmentation. Nevertheless when the cement immediately flows to a superior position from a biomechanical point of view, the amount of injected PMMA can even be further reduced. On the other hand, an augmentation procedure can be halted after injection of 2 ml of PMMA in an undesired direction, making multiple attempts to direct more PMMA to other localisations avoidable. In both situations, the amount of injected PMMA can be reduced to an absolute minimum what will decrease the risk of cement leakage or cartilage damage.

7. Conflict of interest statement

The authors are not compensated and there are no other institutional subsidies, corporate affiliations, or funding sources supporting this work unless clearly documented and disclosed: Synthes GmbH kindly provided the implants and bone cement.

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General discussion and perspectives

1. Hip fracture prevention

Of all fragility fractures, hip fractures constitute the most dramatic complication of osteoporosis. This can be explained by their associated high morbidity, mortality and the health care related costs they induce.[1-5] Furthermore, osteoporotic hip fracture patients are at the highest risk to sustain a secondary osteoporotic fracture.[6] Besides an important evolution in the surgical techniques to treat hip fractures during the last decades[7-10], the care for fragility hip fracture patients has significantly improved with the introduction of clinical pathways and co-managed or orthogeriatric care.[11-14] Despite their positive impact, these interventions mostly focus on in-hospital and short-term results.[15] Because patients with fragility hip fractures are highly susceptible for recurrent fractures, the possible role of the surgeon treating the first fracture should be considered in preventing subsequent fractures. In a first part of this doctoral thesis project, the problem of secondary fracture prevention in the context of a geriatric-traumatologic fracture prevention program was explored.

Chapter I: The impact of care pathways for fragility hip fracture treatment on one year mortality: systematic literature review and meta-analysis.

In this first chapter, a systematic review of the available literature on the subject was performed. As primary research question, the effect of care pathways for fragility hip fracture treatment on the six months and one-year mortality has been checked. Secondary research questions were the prescription of anti-osteoporosis medication and the effect of care pathways on recurrence fracture rate. Four randomized controlled trials[16-19] and seven non-randomized studies[20-26] have been included in a meta-analysis. This meta-analysis could only prove a significant effect of care pathways on one-year mortality for the non-randomized controlled studies. Furthermore, none of the included studies reported recurrent fracture rate and data on antiresorptive therapy were scarce.

With the performance of this meta-analysis, a more uniform evaluation of the existing clinical pathways for fragility hip fracture treatment was realised compared to previously performed studies where different types of orthogeriatric fracture care were included. Due to the rigorous inclusion criteria, only evidence based approaches based on multidisciplinary and integrated care, were withheld. However it was not easy to come to conclusions.

Only a small number of studies could be included reporting on the long-term mortality. Because there were only four randomized controlled trials, it was decided to perform a separate analysis for the seven non-randomized studies that were withheld. We realize that the inclusion of non-randomized trials enlarges the risk of bias and therefore, a critical evaluation of the non-randomized studies was performed. Concerning the influence of clinical pathways on the occurrence of recurrent fragility fractures, only poor information about the administration of anti-osteoporosis medication was found and no data about the occurrence and number of recurrent fractures could be retrieved. Most of the programs focused on peri-operative interventions and were aimed at short-term results.

So this review of the literature and meta-analysis confronts us to some gaps in our current knowledge. Primarily, there is almost no information available in the actual literature on the inclusion of fracture prevention measures in clinical pathways for fragility hip fracture treatment. Secondly, only a few studies report on the possible role of the surgeon treating the first fragility hip fracture in secondary osteoporosis prevention.[27,28] Thirdly, there is an urgent need to document the long-term results of the existing clinical pathways on fragility hip fracture treatment.

Chapter II: The impact of a traumatologic-geriatric post-fracture program for osteoporotic hip fracture patients.

To answer the questions raised after the performance of the meta-analysis of chapter 1, a clinical pathway aimed at the prevention of recurrent fragility fractures was developed, implemented on the traumatology ward and evaluated.

The development of the pathway was performed by a close collaboration between the Traumatology Department and Center for Metabolic Bone Diseases. All patients above the age of 65 who sustained a fragility hip fracture and who were able to come to the center for metabolic bone diseases on an ambulatory base, were included. The following key interventions were performed:

1. The administration of calcium (1000 mg) and vitamin D (800 IU).
2. The systematic referral to the Center for Metabolic Bone Diseases for the evaluation and treatment of the underlying osteoporosis.
3. The providing of information about the clinical pathway to the patient, her / his family and general practitioner.

To evaluate the pathway, a retrospective study was performed by patient chart analysis. Two study groups were created: an intervention group of patients subjected to the program and a historical control group treated by standard care. Demographic, process and outcome parameters for both groups were compared.

A significant difference was observed between the two study groups for all process parameters. However the traumatologic-geriatric post-fracture program did not lead to a significant reduction in the number of recurrent fractures or to a mortality reduction within the first year after the fracture.

With this project, two important innovations were achieved. At first, surgeons treating fragility hip fractures, were actively involved in secondary fracture prevention. With the implementation of the pathway, information sessions were organized for all co-workers of the traumatology department and refresher sessions are being organized on a yearly base to highlight the main points of the pathway. We introduced a sensibilisation for the problem of the underlying osteoporosis: patients with other fragility fractures than hip fractures were informed as well about osteoporosis by our co-workers (medical and paramedical) and an appointment to come to the center for metabolic bone diseases often was provided.

Secondly, in the comparative study, the intended long-term follow-up of one year could be achieved.

The results showed a significant impact of the care pathway on all process parameters (with all $p < 0.001$). This expressed a profound sensibilisation for the problem in all co-workers involved. The same sensibilisation was found within our geriatric patient population, expressed by the relatively high compliance to referral (70.95%). However, a significant impact of the pathway on the number of recurrent fractures and the mortality in the year following the fracture, could not be shown. This is probably due to the relative short follow-up time despite the intended period of one year. When looking at the study results in detail, the mean time for referral to the center for metabolic bone diseases was 77 days or 2.5 months. With a mean follow-up time of 10 months (a one-year follow-up time was achieved for 78.24% of the included patients), the real follow-up time starting from the administration of antiresorptive therapy was only 7.5 months. In the large-scale studies on antiresorptive therapy[29,30], the relative risk reduction of recurrent hip fractures started at 12 months and progressively increased until the end of follow-up at 36 months.

So the non-significant trend in lower numbers of recurrent fractures we observed in our study, might represent the start of a similar evolution.

A first perspective for future research consequently will be to extend the follow-up time of our study. Another perspective will be to include fall evaluations and fall preventive measures in a more standardized way, as falls prevention is an essential component of any strategy aimed at reducing fracture risk in the elderly.[31] A last perspective will be to introduce a general traumatologic-geriatric co-managed care pathway for hip fracture patients. The added value of this program will be to provide structured and integrated care to this frail patient population of elderly hip fracture patients.

2. Hip fracture fixation

Besides the previously described evolution towards co-managed care for fragility hip fracture patients, there has been a simultaneous evolution in implant designs. Although there is no evidence yet that the use of intramedullary implants for the treatment of intertrochanteric hip fractures lead to better outcomes compared to plate and screw systems, there is a trend towards the use of nails and further research on new designs of intramedullary nails aiming at a reduction of peroperative fractures has been encouraged.[9,32,33] Furthermore, there is an evolution towards the use of helically shaped implants instead of screws to fix the proximal fracture fragment.[34,35] Despite the biomechanical advantages of these implants, failures do still occur. Cut-out is one of the most devastating complications and consists of a perforation of the cephalic implant through the femoral head followed by a secondary varisation of the femoral head. Besides surgeon related causes like incomplete fracture reduction and suboptimal implant positioning[36-38], it was found that cut-out is strongly related to the bone quality of the femoral head.[39,40]

In a second part of this doctoral research project, a number of biomechanical investigations have been performed aiming at a better implant fixation in osteoporotic femoral heads. Therefore, the principle of implant augmentation was explored. This principle is based on increasing the implant to bone interface by the addition of bone cement, reducing the stresses on the trabecular structures.

In the past, large amounts of bone cement have been used to fill pre-drilled voids or fracture gaps. Due to the associated complications like delayed or non-unions, thermal necrosis and blocking of the sliding mechanism of the implants, a new technique of augmentation *through* the implant has been developed and tested in three biomechanical studies.

Chapter III: Biomechanical evaluation of bone-cement augmented proximal femoral nail antirotation blades in a polyurethane foam model with low density.

In this study, a polyurethane foam model mimicking osteoporotic bone was used to test cement augmentation of the perforated helical blade of the proximal femoral nail antirotation.[41] Four study groups were created comprising non-augmented and augmented helical blades in a centered and off-centric position. This change in position enabled us to investigate the influence of a biomechanically inferior position of the implant, like it sometimes is noticed in practice. Augmentation was performed with the injection of 3 ml of polymethylmethacrylate (PMMA) through the cannulation and the perforations of the helical blade. By turning the cannula 360° during the PMMA-injection, a circumferential cement distribution around the implant tip was obtained. Subsequently, biomechanical testing of all specimens was performed by the use of a model mimicking an unstable intertrochanteric fracture.[42] The test results clearly showed a better performance of the augmented implants. Secondly, from a biomechanical point of view, augmentation even had a bigger influence in suboptimal implant positions.

The innovative aspects of this study are the possibility to perform the augmentation procedure through the implant without the need to create a void. In this way, it is not possible to miss the correct place for implant insertion. Furthermore, no PMMA leakage can occur at the fracture site because the cement is distributed around the tip of the implant. Finally, there is an important reduction of the risk for avascular necrosis of the femoral head because of the small amounts of PMMA (maximum 3 ml) used as there has been shown a correlation between the amount of PMMA used and the heat production in the bone surrounding the PMMA.[43]

Nevertheless, a lot of concerns rose when extrapolating these testing results to clinical practice.

At first, a perforation of the femoral head by drilling the K-wire could lead to cement leakage into the hip joint. Secondly, until now, we do not have an instrument at our disposition to measure the quality of the bone peroperatively. This means that the decision to augment or not, completely depends on the findings of the surgeon performing the procedure. Thirdly, there are some concerns about implant removal. Can the extraction of an augmented implant cause problems in practice: will the cement shear off the implant and will it be possible to drill through PMMA remnants? Finally, implant augmentation is used to enhance the implant to bone interface reducing thereby the risk of implant failure due to osteoporosis. The even better results of augmentation of implants in biomechanically less favourable positions, could encourage surgeons to accept mal-positioning of implants and to use augmentation as a solution for bad surgery what was not intended at all.

Chapter IV: Potential of PMMA cement-augmented helical PFNA blades to improve implant stability - a biomechanical investigation in human cadaveric femoral heads.

In this study, an equal biomechanical testing as in the study on foam models was performed on study groups of non-augmented and augmented helical blades implanted in cadaveric femoral heads.[44] Before implantation of the helical blades, bone mineral density was measured by peripheral quantitative computed tomography (pQCT) and only cadaveric bones with a bone mineral density representative for the overall elderly population, were included. When performing the augmentation procedure in cadaveric bones, it was noticed that a more heterogeneous cement distribution around the implant was achieved despite the fact that the same standardized technique of circumferential PMMA injection was used in all test specimens. Nevertheless, the study results showed that the augmented specimens performed biomechanically better than the non augmented ones. Furthermore, it was clear that the effect of augmentation was reduced with increasing bone quality, suggesting that PMMA augmentation is primarily useful in the most osteoporotic bones.

This biomechanical study on a cadaver model brought the technique of implant augmentation closer to clinical practice.

Following the technical problems occurring when performing the augmentation procedure of helical blades in cadaveric bones, the following adaptations where made to the instruments: stronger syringes and a calibrated plunger were provided to allow the surgeon to inject the PMMA by hand pressure.

After publication of the biomechanical testing results, only half of the amount of PMMA was provided in the package to perform the procedure as an amount of 3 ml of bone cement increases the anchoring capacity of the implants significantly and the risks associated to the use of excessive amounts of PMMA can be prevented.

Furthermore, a market preference evaluation called "Market preference evaluation augmented PFNA" was performed to evaluate the technical performance and the early clinical results of this new technique. The University Hospitals Gasthuisberg participated in this study with study number S52004 with the inclusion of one patient. This allowed us to bring the technique of implant augmentation to clinical practice.

Prior to augmentation, a leakage test was performed to exclude perforations of the femoral head to prevent intra-articular leakage of the PMMA. The results of this first clinical study about PFNA augmentation proved the feasibility of a standardised augmentation technique.[45] Blade migration was prevented and good functional results were achieved. No major complications were encountered and it was feasible to remove the augmented implant if necessary as was shown by some cases.

Thereafter, a randomized controlled trial was performed called "Proximal Femoral Nail Antirotation (PFNA) versus PFNA augmentation: comparison of PFNA versus PFNA augmentation for the treatment of closed unstable trochanteric fractures - a randomized controlled trial". The University Hospitals Leuven participated in this trial as well with study number S54141 with the inclusion of 28 patients. It was the primary purpose of this study to evaluate if PFNA augmentation leads to a better stability by facilitating early mobilization and full weight-bearing with less pain. As an addendum to the clinical study, an intra-operatively bone density measurement was added. This measurement was performed by a torque measurement tool, called DensiProbe^{TM} (ARI, Davos, Switzerland). This is an important step because there is an urgent need to clearly state the indications for implant augmentation. As most of the fragility hip fracture patients don't have a DEXA-scan available indicating their bone quality at the moment they sustain their fracture, the decision to augment or not completely depends on the personal judgement of the surgeon.

It would be a big advantage to have the possibility to perform an objective bone density measurement during the surgical procedure to avoid unnecessary augmentation procedures. So we expect the need to clearly state the indications for augmentation to be solved after the validation of the DensiProbe^{TM} measuring results. The inclusion and follow-up of the patients in the randomized controlled study have been performed and study results are being calculated and will be available soon.

The only concern still remaining is the unpredictable cement distribution in osteoporotic bone. Both clinical trials showed a relatively homogeneous cement distribution. However it was not possible to guide the cement to a desired direction, sometimes giving rise to unfavourable localisations like for instance more to the subchondral areas. This finding encouraged us to set up a third biomechanical study evaluating this problem.

Chapter V: Cement augmentation of hip implants in osteoporotic bone: how much cement is needed and where should it go?

In this third biomechanical study on augmentation of the PFNA helical blade, different localizations and amounts of PMMA around the implant were tested.[46] The same foam model and testing technique as in the two previous biomechanical studies were used.[41,44]

Six study groups of foam specimens simulating osteoporotic bone were created. In each group, a different amount and localisation of PMMA in relation to the helical blade was injected. This was possible due to the homogeneous character of the foam model, allowing for a well-targeted cement distribution. Furthermore, a benchmark of six cadaveric femoral heads instrumented with a non-augmented helical blade, was created. The bone quality of these cadaveric bones was measured by peripheral quantitative computer tomography and evaluated as good or non-osteoporotic.

The biomechanical testing results clearly showed that both the localisation and the amount of PMMA do have an influence on implant purchase. Furthermore, the study showed that any configuration and amount of PMMA used, leads to a biomechanical stability of the construct comparable to the stability of the non-augmented cadaveric benchmark which was set as a reference point.

Finally, biomechanically more superior localisations of PMMA could be identified and were localised cranial to the blade and at the blade tip.
These study results again will have an influence on clinical practice. At first, they will allow surgeons to further reduce the amount of PMMA used, thereby reducing the risks for cement leakage and cartilage damage. Furthermore, the results will allow surgeons to stop the augmentation procedure when the PMMA flows to less desirable localisations and make multiple attempts to guide it to another direction unnecessary.

Implant augmentation of the proximal femur as investigated in the above described biomechanical and clinical studies, only is the first application of a surgical technique that leads to a lot of opportunities that can be further explored. As an adjunct to the clinical studies on implant augmentation of the proximal femur, a cost/benefit analysis, balancing the potential to reduce the 3.6% failure rate with the cost and the potential risks of the use of PMMA cement, could be performed.
Furthermore, the technique of implant augmentation in the proximal femur can be extrapolated to other bones susceptible for fragility fractures. Biomechanical studies have already been performed on implant augmentation in the distal femur and in the proximal humerus. In the distal femur, augmentation of the distal screws of a locking plate has been performed with 1ml of PMMA per screw before screw insertion. Study results showed an increased stability for the osteoporotic bone model; augmentation did not influence the stability of the construct in a non-osteoporotic bone model.[47,48]
Besides for the distal femur, the principle of injecting cement through a cannulated implant has been applied for the proximal humerus as well. In a first biomechanical study[49], the feasibility of augmentation through the cannulated and perforated screws of a proximal humerus locking plate has been evaluated. The study results showed an increased anchorage of the augmented implants. In a second biomechanical study on implant augmentation of the proximal humerus[50], the augmentation was limited to the two screws in the region of the lowest bone density thanks to the use of DensiProbe™, an instrument allowing for local bone quality determination by mechanical torque. The study results once again showed that implant augmentation led to a significant improvement in primary stability and the use of DensiProbe™ allowed for a more selective and limited use of PMMA.

For the moment, a first clinical study on implant augmentation of the proximal humerus (augmentation of the Philos proximal humerus plate) is running.

Another perspective following the promising results of our biomechanical studies on implant augmentation could be to modify the composition of the bone cement to make it more similar to normal, healthy bone. Primarily, the PMMA as used so far is rather brittle and has elastic properties that are completely different from those of normal bone. It would be very challenging to adjust the composition of the cement to create one with exactly the same elastic properties as normal bone.

Furthermore, the possible toxic effects of PMMA and the exothermic reaction when hardening, remain concerns that still need to be solved.

Finally, when starting to think about changing the mechanical and chemical properties of the bone cement, the idea to use the principle of augmentation in an intact femur as a mechanical prophylaxis to prevent fragility fractures, can be further explored. A first biomechanical study has been performed on this subject evaluating a V-shaped cement augmentation of the proximal femur.[51] In five pairs of proximal femora, one specimen of each pair was augmented by a minimal invasive approach. A diverging V-shaped cement volume (PMMA) was injected in the superior and inferior femoral neck through only one entry point in the lateral cortex with the aim to reinforce the areas exposed to the highest stresses during a fall. Clinical relevant fractures could be generated by a dynamic fall set-up simulating a sideways fall. The test results showed increased energy absorption of the augmented specimens carrying the potential to prevent secondary fractures. Compared to previously performed studies on this subject, the amount of PMMA used could be limited, decreasing the possible side-effects like toxicity and thermal effects and the procedure could be performed in a minimally invasive way. The promising results of this study encourage further research on the subject, possibly comprising further adjustments to cement configuration.

3. Conclusion

It was the aim of this doctoral research project to address the problems of fracture fixation and prevention in osteoporotic bone.

Concerning fracture prevention, the clinical study on the implementation and the evaluation of a traumatologic-geriatric post-fracture program preventing recurrent fractures, led to an impact on process outcomes correlated with good postoperative care for hip fracture patients and a sensibilisation of health care professionals and patients to this growing problem. However, larger studies with a longer follow-up are needed to evaluate the effect of the program on outcome parameters like long-term mortality and recurrent fracture rate.

Concerning fracture fixation in osteoporotic femoral heads, the augmentation studies showed a clear benefit of cement augmentation on implant purchase and are a perfect illustration of experimental research being brought to clinical practice, leading to an amelioration of the operative outcomes in a frail patient population. This is illustrated by figure 1. Due to its favourable results, the principle of implant augmentation opens a lot of opportunities for further research.

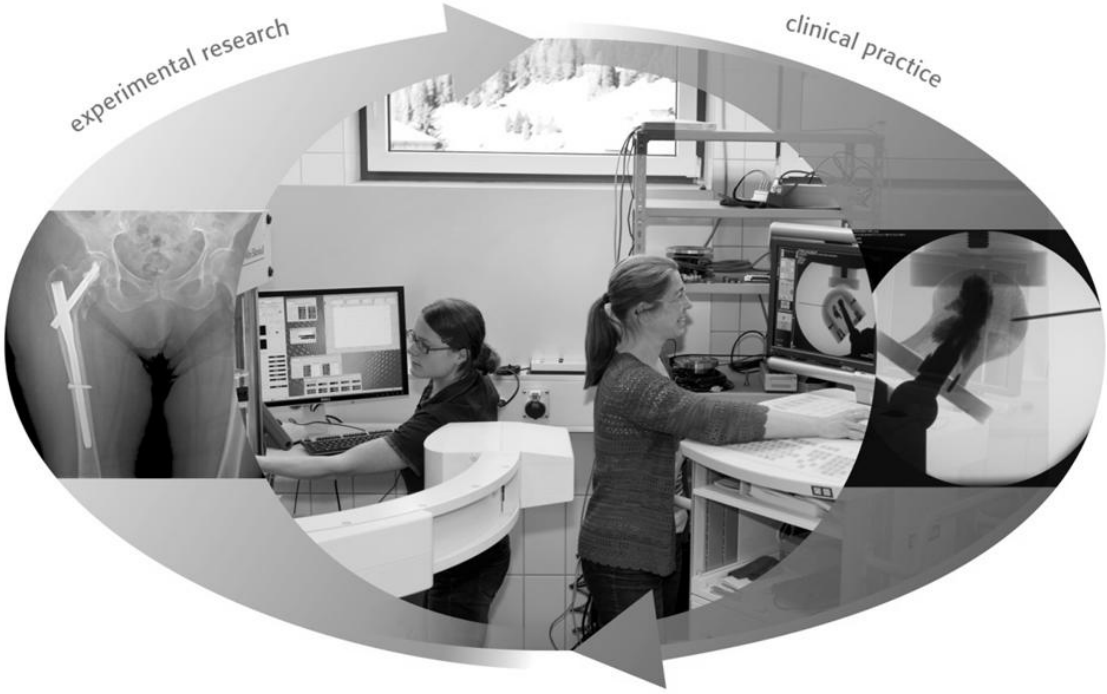

Figure 1: Interlinking experimental research to clinical practice (AO-Dialogue 2011; 2: 11)

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Summary

During the last decades, a tremendous increase in osteoporosis related hip fractures has been noticed. It is expected that this evolution will continue due to the expanding life expectancy and due to the active aging of our population. From a clinical perspective, the consequences of fragility hip fractures are devastating: they lead to a high morbidity and mortality and include a high risk for secondary fractures. From an economic perspective, they lead to an associated increase in health care related costs.

These findings point to important gaps in our current knowledge and define major research priorities. First of all, there is the clinical requirement to implement integrated referral pathways that will improve secondary fracture prevention. While it is clear that surgeons play a pivotal role in managing fracture patients, few research initiatives attempted to optimize post-fracture osteoporosis management by a surgeon-driven team. Secondly, there is an urgent need for interventional research to develop strategies that enhance fixation stability in the osteoporotic proximal femur. Despite an evolution in the surgical techniques to treat fragility hip fractures, failures of fixation do still occur. Cut-out is one of the most devastating complications and consists of a perforation of the cephalic implant through the femoral head followed by a secondary varisation of the femoral head. Besides surgeon related causes like incomplete fracture reduction and suboptimal implant positioning, it was found that cut-out is strongly related to the bone quality of the femoral head.

The aim of the current doctoral research program was to address both priorities. In a first part (Chapter I and II), the development and the testing of an integrated secondary fracture prevention program was addressed. In a second part (Chapter III, IV and V), the development and biomechanical testing of a new surgical technique to improve implant fixation in the osteoporotic femoral head was addressed.

In **chapter I**, a review of the literature and meta-analysis was performed on the impact of care pathways for fragility hip fracture treatment on one-year mortality. There was a significant effect of care pathways on one-year mortality for the seven included non-randomized controlled studies. None of the included studies reported recurrent fracture rate and only poor information about the administration of anti-osteoporotic medication could be found. Most of the studies focused on peri-operative interventions and were aimed at short-term results.

In **chapter II**, a traumatologic-geriatric fracture prevention program was set up. This care pathway was developed in a close collaboration between surgeons and geriatricians and included three key interventions. Primarily, calcium and vitamin D was administered to all included patients. Secondly, the patients were referred to the Center for Metabolic Bone Diseases (CMBD) for the evaluation and the treatment of the underlying osteoporosis. Finally, information about the fracture prevention program was provided to the patient, her / his general practitioner and family.

A retrospective study was performed to evaluate the process and outcome parameters. This study showed a clear impact on the process outcomes with a high uptake of calcium and vitamin D by the fracture patients, a high compliance with the referral to the CMBD and a sensibilisation of all included patients and health care professionals involved. Nevertheless, no impact of the program could be shown on the long-term mortality nor on the recurrent fracture rate.

In the remaining chapters, three biomechanical studies on implant augmentation of the proximal femur were addressed. The principle of implant augmentation is based on an increase of the implant to bone interface by the addition of bone cement. In our studies this was done through the cannulated and perforated helical blades of the Proximal Femoral Nail Antirotation.

In **chapter III**, a first biomechanical evaluation of bone-cement augmented Proximal Femoral Nail Antirotation blades was performed on a polyurethane foam model mimicking osteoporotic bone. The test results clearly showed a better performance of the augmented implants compared to the non augmented ones. Secondly, augmentation even had a bigger influence on constructs with suboptimal implant positioning.

In **chapter IV**, the same biomechanical tests were performed on osteoporotic human cadaveric femoral heads. In this study, the augmented specimens performed biomechanically better than the non-augmented ones as well. Furthermore, the study showed that the effect of augmentation was reduced with increasing bone quality, suggesting that augmentation is primarily useful in the most osteoporotic bones. When performing the augmentation procedures, it became clear that a more heterogeneous cement distribution around the implant was achieved in cadaveric bones compared to the foam models.

This last finding was further explored in **chapter V**. In this third biomechanical study, different localisations and amounts of bone cement around the implant were tested, again on a foam model mimicking osteoporotic bone. The testing results clearly showed that both the localisation and the amount of cement do have an influence on implant purchase. Furthermore, the study showed that any configuration and amount of bone-cement used, led to a biomechanical stability of the construct comparable to the stability of a non-augmented cadaveric benchmark which was set as a reference point. Finally, biomechanically more superior localisations of cement could be identified and were localised cranial to the blade and at the blade tip.

To conclude, both clinical and biomechanical studies could prove their impact on osteoporotic hip fracture treatment. Concerning fracture prevention, the clinical study on the traumatologic-geriatric post-fracture program led to a sensibilisation of health care professionals and patients for this growing problem. However, larger studies with a longer follow-up are needed to evaluate the effect of the program on outcome parameters like long-term mortality and recurrent fracture rate.

Concerning fracture fixation in osteoporotic femoral heads, the augmentation studies showed a clear benefit of cement augmentation on implant purchase. Due to these favourable results, the principle of implant augmentation opens a lot of opportunities for further research. In addition, the biomechanical studies are a perfect illustration of experimental research being brought to clinical practice, as the first clinical studies on implant augmentation of the osteoporotic femoral head are running. The promising results of both our clinical and biomechanical studies might ameliorate the outcomes of this frail patient population suffering from osteoporotic hip fractures.

Samenvatting

Ten gevolge van het steeds ouder worden van onze populatie, neemt het aantal personen met osteoporose evenals het aantal osteoporose gerelateerde heupbreuken toe. Van uit klinisch standpunt zijn de gevolgen van een osteoporotische heupbreuk desastreus: dergelijke fracturen kennen een zeer hoge morbiditeit en mortaliteit en omvatten een reëel risico op recidieffracturen. Van uit economisch standpunt leiden osteoporotische heupfracturen tot een enorme toename van de kosten in de gezondheidszorg.

Deze gegevens duiden op twee belangrijke tekortkomingen in onze huidige kennis en onderzoeksprioriteiten. Ten eerste is er de klinische noodzaak om op een systematische wijze geriatrische heupfractuurpatiënten te includeren in een programma om recidieffracturen te voorkomen. Tot op de dag van vandaag beperken chirurgen zich tot het stabiliseren van de botbreuken en hebben zij geen of slechts beperkte aandacht voor de behandeling van de onderliggende osteoporose. Ten tweede is er de dringende noodzaak om strategieën en technieken te ontwikkelen om een betere fixatie van implantaten in de osteoporotische heupkop te verkrijgen. Ondanks een reeds doorgemaakte evolutie in de heelkundige technieken om osteoporotische heupbreuken te stabiliseren, treden er nog vaak complicaties op in de geriatrische patiëntenpopulatie. Het doorbreken van het implantaat doorheen de osteoporotische heupkop is een gevreesde verwikkeling dewelke aanleiding geeft tot secundaire varisatie van de heupkop. Naast een onvoldoende reductie van de fractuur en een suboptimale positie van het implantaat, speelt onderliggende osteoporose een belangrijke rol bij het optreden van deze complicatie.

Het was de doelstelling van dit proefschrift om beide prioriteiten te behandelen. Als dusdanig werd de secundaire preventie enerzijds en de fixatie van heupfracturen bij de oudere patiënt anderzijds bestudeerd. In een eerste gedeelte van dit proefschrift (hoofdstuk I en II) werd de secundaire preventie van heupbreuken behandeld. In een tweede gedeelte van het proefschrift (hoofdstuk III tot V) werd een nieuwe chirurgische methode bestudeerd om implantaten in een osteoporotische heup te fixeren.

Heupfractuurpatiënten lopen een groot risico om nieuwe osteoporotische breuken op te lopen. In het eerste gedeelte van ons onderzoek werd een programma om nieuwe breuken te voorkomen, ontwikkeld en geëvalueerd.

In **hoofdstuk I** werd een systematisch literatuurnazicht uitgevoerd over dit onderwerp. Dit nazicht toonde aan dat de meeste studies zich enkel richten op korte termijn resultaten en dat ze geen informatie verschaffen over het optreden van secundaire fracturen noch over maatregelen om nieuwe breuken te voorkomen. In de meeste studies werden enkel interventies voorgesteld gedurende de peri-operatieve periode en werden enkel korte termijn resultaten nagestreefd.

In **hoofdstuk II** werd een programma voorgesteld om nieuwe breuken te voorkomen. Dit programma is gebaseerd op de samenwerking van de chirurgen die de heupbreuk behandelen en de geriaters, die zich richten tot de oudere patiënten in het algemeen. Alle patiënten die in het programma geïncludeerd werden, kregen calcium en vitamine D en werden verwezen naar het Centrum voor Metabole Botziekten van de UZ Leuven voor een evaluatie en behandeling van de onderliggende botontkalking. Daarnaast werden de patiënten zelf, hun familie en hun huisarts op de hoogte gebracht van het programma. Deze studie leidde tot een duidelijke sensibilisatie van zowel patiënten als gezondheidsmedewerkers voor het probleem maar de studie kon de overleving na één jaar noch het optreden van nieuwe breuken voorkomen.

Ten gevolge van de slechte kwaliteit van het bot, is het niet altijd even gemakkelijk om osteoporotische heupbreuken chirurgisch te behandelen. In een tweede deel van dit proefschrift werd het gebruik van cement voor het beter verankeren van een implantaat in ontkalkt bot, geëvalueerd. Dit gebeurde door middel van drie biomechanische studies.

In **hoofdstuk III** werd de toevoeging van cement aan een schroef om de heupkop beter te fixeren, op een kunststof model getest. De studieresultaten toonden duidelijk de gunstige effecten aan van de toevoeging van cement op de fixatie van de schroef.

In **hoofdstuk IV** werden dezelfde testen uitgevoerd op heupbeenderen afkomstig van een overleden menselijk lichaam. Dezelfde gunstige testresultaten werden bekomen zoals in de studie op het kunststof model. Bijkomend werd vastgesteld dat de toevoeging van cement aan het implantaat het meeste effect had in het bot met de slechtste kwaliteit. Tenslotte werd vastgesteld dat de verspreiding van het cement in de menselijke heupkop meer heterogeen was.

In **hoofdstuk V** werden verschillende lokalisaties en hoeveelheden cement vergeleken in een kunststof model. The studieresultaten toonden aan dat bepaalde lokalisaties gunstiger waren dan andere. Daarnaast toonde de studie aan dat het aanbrengen van cement op iedere lokalisatie aanleiding gaf tot een even stabiele constructie als een gelijkaardige constructie zonder cement in normaal (niet ontkalkt) bot. Vanuit biomechanisch standpunt situeerden de beste lokalisaties zich craniaal van het implantaat of ter hoogte van de tip van het implantaat.

Om te besluiten kunnen we stellen dat zowel de klinische als de biomechanische studies een gunstig effect aantoonden op de behandeling van osteoporotische heupbreuken. Voor wat betreft de preventie van recidief fracturen toonde de klinische studie aan dat de systematische aanpak van de onderliggende osteoporose door de chirurg, aanleiding gaf tot een sensibilisatie van zowel de patiënten als de gezondheidsmedewerkers voor dit groeiend probleem. Voor wat betreft de fractuurfixatie in de osteoporotische heupkop, toonden de biomechanische studies het gunstige effect van augmentatie op de stabiliteit van de constructie aan. Deze veelbelovende resultaten zullen ons toelaten de postoperatieve complicaties en kwaliteit van leven bij deze kwetsbare populatie van patiënten met een gebroken heup verder te verbeteren.

Curriculum Vitae

An Sermon

Personal Information

Name: An Sermon
Date of birth: 28/08/1973
Place of birth: Ukkel, Belgium

Education

1985 - 1991	Secondary education: Latin-Greek, Heilig Hartinstituut, Halle
1991 - 1998	Medical Sciences (graduated cum laude), Katholieke Universiteit Leuven
1998 - 2004	Specialisation General Surgery, Katholieke Universiteit Leuven
2004 - 2006	Specialization Traumatology, Katholieke Universiteit Leuven
2009 - 2014	Doctoral training, Doctoral School Biomedical Sciences, Katholieke Universiteit Leuven

Professional experience

01/08/2004 - 31/07/2006	Resident in the department of Traumatology, University Hospitals Leuven, Belgium
01/08/2006 – 31/07/2007	Supervisor in the department of Traumatology, University Hospitals Leuven, Belgium
01/08/2007 - present	Joint clinical head in the department of Traumatology, University Hospitals Leuven, Belgium
01/09/2009 – present	Senior research fellow, AO Institute, Davos, Switzerland

Member of:

- KWS Adviesraad
- Multidisciplinair Wondteam
- Stuurgroep Vaardigheden
- Stuurgroep Spoedgevallen
- Raad van Bestuur LUMOS (Leuvense Universitaire Medische Ontwikkelingssamenwerking en Solidariteit)
- Werkgroep Kameroen (onderdeel van LUMOS)
- Werkgroep Palliatieve Zorg
- Bestuurscomité UZ Leuven

Assignments at KUL:

- E04L6a: Keuzetopics: Principes van heelkundige fractuurbehandeling
- E06L8a: Probleemoplossend Klinisch Redeneren (Masterproef deel 2): Polytrauma
- L04F6a: Selected topics in Musculoskeletal Pathology: New trends in traumatology - State of the art
- E00L9a: Semiologie menselijk bewegingsstelsel: onderste lidmaat
- E05Y0a: EHBO en verbandleer: practicum
- E06L7a: Geïntegreerd klinisch onderzoek en redeneren (Stationsproef) (Masterproef deel 1)

Professional qualifications

Certificate of Acute Medicine (27/04/2000)

Post-academic course on radioprotection, diagnostic use of X-rays (10/07/2002, Ghent University, Belgium)

AO courses:

- Principles of Operative Fracture Treatment (2003)
- Rationale of Pelvic and Acetabular Fracture Care (2003)
- Advances in Operative Fracture Management (2004)
- AO Trauma Course – Geriatric Fractures (2009)
- AO Trauma Course – Polytrauma (2009)

ATLS Provider Course (03/01/2010, Riel, The Netherlands)

ATLS Generic Instructor Course (23/03/2010, Riel, The Netherlands)

Opleiding Kwaliteitszorg, module Klinisch Onderzoek (2010-2011, KUL)

Opleiding Ziekenhuisfinanciering (2011-2012, KUL)

Opleiding Leiderschap voor Medische Stafleden (2012-2013, UZLeuven)

Professional memberships

Belgian Trauma Society (BTS)

Royal Belgian Society for Surgery (RBSS)

European Society of Trauma and Emergency Surgery (ESTES)

AO Trauma

Scientific publications

Articles in internationally reviewed academic journals

Sermon A, Hofmann-Fliri L, Richards R, Flamaing J, Windolf M. Cement augmentation of hip implants in osteoporotic bone: how much cement is needed and where should it go? J Orthop Res 2014 Mar; 32(3): 362-8

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Articles in other academic journals

Boonen S, Lioen P, Sermon A, Gielen E, Laurent M, Borghs H, Vanderschueren D, Grootaert V, De Keulenaer J, Spriet I, Rademakers F, Luyten F. Atypische dijbeenfracturen in het kader van een langdurige bisfosfonaatbehandeling. Tijdschrift voor Geneeskunde 2012; 68(11): 531-538

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Sermon A, Gruwez JA, Lateur L, De Wever I. The Importance of Magnetic Resonance Imaging in the Diagnosis and Treatment of Diffuse Lymphangioma. Acta Chir Belg, 1999; 99: 230-235

Academic book chapters

Sermon A. Pertrochanteric fractures: cement augmentation. In: Rommens PM, Hessmann MH (eds.). Intramedullary nailing: a comprehensive guide. Springer London 2015 (in press)

Meeting abstracts presented at scientific conferences and symposia

Sermon A, Herteleer M, Boonen S. Clinical pathway "Prevention of fragility fractures": development, implementation and preliminary results. Oral presentation at the annual congress of the European Society of Trauma and Emergency Surgery (06/05/2013, Lyon, France)

Sermon A, Fliri L, Richards R, Boonen S, Windolf M. Augmentation of hip implants in osteoporotic bone: how much cement is needed and where should it go? Oral presentation at the annual congress of the European Society of Trauma and Emergency Surgery (14/05/2012, Basel, Switzerland)

Sermon A. Latest implant technology: from screws to augmented blades. Oral presentation at Osteologie (31/03/2012, Basel, Switzerland)

Sermon A, Herteleer M, Boonen S. Clinical pathway "Prevention of fragility fracture recurrences": development, implementation and preliminary research. Oral presentation at BVOT Spring Symposium (24/03/2012, Leuven)

Gebhard F, Sermon A. 15/12/2011: PFNA augmentation: biomechanical aspects. Oral presentation at the "Meet the experts symposium", AO Trauma courses (15/12/2011, Davos, Switzerland)

Sermon A, Fliri L, Windolf M. PFNA Augmentation: Biomechanical study on PMMA localization. Oral presentation at the AO Trauma 6th General Meeting Clinical Priority Program Fracture Fixation in Osteoporotic Bone (27/05/2011, Munich, Germany)

Sermon A. AO Guest Lecture: Implant augmentation: From experimental research to clinical application. Oral presentation at AO Research Institute (02/05/2011, Davos, Switzerland)

Sermon A. Complications and solutions in intertrochanteric fracture fixation. Oral presentation at AO Symposium: "Failures, complications and solutions in geriatric fracture surgery" (29/01/2011, Luxembourg, Luxembourg)

Sermon A. Implant augmentation of the proximal femur: from the identification of the right indications to the surgical technique and the prevention of complications.

Hip fractures: is there a place for plate and screw osteosynthesis?

Distal radius: the plates techniques. Oral presentations at the annual congress of the BOTA (Belgian Orthopaedic and Trauma Association) (18/09/2010, CHU Mont Godinne, Belgium)

Sermon A. Implant augmentation of the proximal femur.

Sermon A, Wähnert D, Boner V, Schwieger K, Windolf M. Potential of cement augmentation of PFNA blades with regard to cut-out resistance: human cadaveric test. Keynote lecture and oral presentation at the annual congress of the European Society of Trauma and Emergency Surgery (16/05/2010, Brussels, Belgium)

Sermon A. Biomechanical testing of PFNA augmentation: how to prevent complications? Oral presentation at AO Clinical Priority Program Fracture Fixation in Osteoporotic Bone, Annual meeting (25/03/2010, Basel, Switzerland)

Sermon A, Broos P. Trends in trauma teaching: failures of fixation of intertrochanteric hip fractures: what have we learned? (oral presentation)

Sermon A, Nijs S, Broos P. New implants for the treatment of distal radius fractures: advantages, pitfalls and complications. (oral presentation)

Sermon A, De Schepper M, Broos P. The use of the helical blade for the stabilisation of intracapsular hip fractures. (poster) presented at the annual congress of the European Society of Trauma and Emergency Surgery (24/05/2008, Budapest, Hungary)

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Sermon A, Reynders P, Broos P. Twin Hook versus Dynamic Hip Screw: preliminary results of a comparative study. Oral presentation at the annual congress of the Belgian Orthopaedic Trauma Association (BOTA) (20/11/2004, Leuven, Belgium)

Broos P, Sermon A. The role of arthroplasty in the treatment of unstable intertrochanteric fractures. Oral presentation at the 6th congress of the European Association for Trauma and Emergency Surgery (09/09/2004, Rotterdam, The Netherlands)